[SEPTEMBER, 1925.]

BRAIN.

PART 3, VOL. 48.

HEPATO-LENTICULAR DEGENERATION.

BY STANLEY BARNES

AND

E. WESTON HURST.

INTRODUCTION.

IT was in 1912 that S. A. K. Wilson [45], in a monograph of outstanding importance, first described under the title "Progressive Lenticular Degeneration" a series of cases of extrapyramidal disease in which cirrhosis of the liver was associated with gross damage of the lenticular nuclei. In this paper he was able to distinguish a sharply defined disease, and to link up the nervous symptoms with the lesions found in the central nervous system.

Since that date many other cases have been recorded, and in its main conclusions his work has received ample corroboration. Recently, however, cases have been published under various titles in which lenticular disease has been found but in which the clinical symptoms differed considerably from those described by Wilson; others, previously reported but reviewed in the light of Wilson's results, showed cirrhosis of the liver but presented symptoms which did not harmonize fully with the Wilson picture. More particularly pseudo-sclerosis and torsion-spasm have constituted a difficulty, and though some authors, notably Hall [17], have grouped these cases with Wilson's, yet the latter, as we read his recent work [46, 47], is still of opinion that they should be regarded as diseases distinct from progressive lenticular degeneration. The relationship between the nervous lesions and the liver disease has provoked much discussion, and the extraordinary absence in the majority of cases of symptoms attributable to the cirrhosis has been a source of some difficulty. Finally, in Wilson's disease, the occurrence of that curious zone of pigmentation of the cornea known as the Kayser-

Fleischer line has been noticed on only one occasion, though it has been described on several occasions as a feature of the other disease conditions.

We have been fortunate in being able to observe over a period of three years four cases in one family, in two of which post-mortem examinations have been made under good conditions. No one reading the succeeding account will fail to conclude that all the four members of this family have suffered from but one form of disease; yet in two of them (one still alive) no nervous phenomena of a degree severe enough to produce objective signs have been present. All of them have suffered from cirrhosis of the liver, and one of them (still living) shows the Kayser-Fleischer line.

Three of the four cases recorded here were shown at the Neurological Section of the Royal Society of Medicine in London in January, 1924. On that occasion we were able to demonstrate that two of the cases were already suffering from extrapyramidal nervous lesions, whilst the third case (E. B.) was in the pre-nervous stage but showed cirrhosis of the liver with ascites and a slight degree of nephritis. By a happy chance Wilson was himself present and agreed that the two cases were suffering from progressive lenticular degeneration.

The task of keeping in close touch with the family has been greatly facilitated by the successive house-physicians of one of us (S. B.). We desire here to record our thanks to them, notably to Dr. Cochrane who was kind enough to make visits to the patients' home and report on the family, and to Dr. A. J. Davies to whom we are indebted for many of the photographs.

We have to thank Professor Haswell Wilson for his care in the earlier post-mortem work; Dr. W. T. Hillier, the Clinical Pathologist at the General Hospital, Birmingham, for the care taken on many occasions in supervising and carrying out the tests for liver efficiency and the gastro-analysis; and Mr. T. Harrison Butler for the beautiful coloured drawings he made when kind enough to report on the corneal pigmentation. To Dr. J. G. Greenfield also we wish to express our thanks for his great assistance and helpful criticism in the pathological investigation, most of which has been carried out in the Pathological Laboratory at the National Hospital, Queen Square. Finally, one of us (E. W. H.) desires to acknowledge the assistance afforded by the Medical Research Council, owing to which it was possible to make a complete histological examination of the fatal cases.

The family.—As far as can be ascertained both the father and mother are healthy in a general sense, neither of them having suffered from any serious disease. The father has two half-brothers living, both of them said to be normal; one full brother died of accident in childhood. No relative of his of whom he has known has ever suffered from any form of progressive paralysis.

The mother has suffered since puberty from periodic migrainous headaches, never severe enough to incapacitate her from work. None of her relations has suffered from any nervous disease.

The children have numbered eight in all, and there have been no miscarriages. The three eldest (a boy, aged 19, a second boy, aged 17, and a girl, aged 16) are all healthy, and without evidence of either nervous or liver disease. The fourth child, Phœbe B. (aged 14), is the second case to be described later. Of the other children, Frederick B. (Case 1) died at the age of 12; Elsie B. (Case 3) died at the age of 10; Daniel B. (Case 4) is 9 years old and has cirrhosis of the liver, whilst the eighth child, now nearly 3 years old, has no nervous symptoms, but when last examined (in 1923) had a palpable liver edge which was considered by Dr. Cochrane to be too hard.

In both parents and in several of the children, the blood has been examined by the Wassermann test; it has been uniformly negative. No sign of syphilis is present in any member of the family.

Case 1.—Frederick B. On July 10, 1922, when 8 years of age, this boy first came under my notice. He was brought to the out-patient department of the General Hospital, Birmingham, his mother complaining that he was losing the use of his right hand and that he dragged his right leg. Admission to the hospital was refused at that time, so it was not possible to make a full record of his state, and only a few rough notes remain of his condition that day. He was a small boy who walked in easily, holding his mother's hand. His facial expression in repose was unusual, for the mouth was constantly kept open (despite the absence of adenoids and the presence of a clear airway through the nose), and its angles were slightly raised, while a little puckering of the eyelids, the merest suggestion of closure, gave the impression that he was always on the verge of a broad smile, and that he had less than the usual degree of emotional restraint.

The condition of the right arm attracted most attention. This was free from involuntary movement (tremor, athetosis, &c.) during rest, was nowhere wasted and could perform all movements with good power. But all voluntary efforts of the right upper extremity were slow, particularly those of its peripheral segments. He could move the arm at the shoulder in all directions, could flex and extend at the elbow, wrist and fingers; but all of these movements, and especially those of the fingers and hand, were performed clumsily and rather stiffly. The outstanding feature was his grip. When given the observer's fingers to clasp, the action was performed powerfully (with a considerable grimace) and completely; but when told "now loose," he relaxed his grip so slowly that some three seconds were required before the observer's fingers were released; he would, if allowed, always attempt to unclench his flexed fingers

by the aid of his left hand. No similar condition occurred when he gripped with the left hand; here relaxation occurred at a normal rate, so that it was evident that the myotonic type of grip with the right hand was not due to lack of understanding on his part. While a grimace occurred whenever he gripped forcibly with his right hand, the effort to unclasp brought forth what can fairly be described as a facial contortion, expressive of pain, anxiety and distress that he should be so slow in obeying the order. His gait was almost normal, a little clumsiness and shuffling with the right leg not being considered definitely pathological.

Further examination of his nervous system showed nothing abnormal, the plantar reflexes in particular being of the flexor type. There is no record of the viscera having been examined.

I was puzzled as to the diagnosis in this case; the outstanding feature was his myotonic grip, and I (S. B.) naturally thought that this might be a case of Thomsen's disease (myotonia congenita). But the condition was almost if not quite confined to the right upper extremity, and there was no history which could have suggested any family history of myotonia. The other possibilities considered were either (1) Wilson's disease, (2) pseudo-sclerosis, (3) congenital damage to the basal nuclei (congenital chorea, &c.), or (4) some acquired damage of the lenticulo-striate region, such as may occur with tumour, infantile hemiplegia or encephalitis lethargica. No definite diagnosis was arrived at on this occasion; the history obtained below became available only several months later.

He was brought up to hospital again on account of increasing disability, particularly in that he was more clumsy with his right hand and arm, and that he was walking worse; he was admitted to the General Hospital, on November 8, 1922. It was then discovered that he had previously (in December, 1919) been an in-patient of the Children's Hospital, Birmingham and that notes on his condition at that time were available. The following account of his previous history was provided partly by the mother and partly by the kindness of Dr. Ball, who was in charge of the boy at the Children's Hospital in 1919.

Previous history.—Until the year 1918, when he was 5 years old, his physical condition had been normal for a boy of his age and social condition. At birth no abnormality had been observed in weight or nervous condition; he cut his teeth and began to talk and walk at the usual age; he had had measles but no other infantile disease.

During his sixth year (January to December, 1919) he suffered from recurring attacks of diarrhœa which were never sufficiently severe for medical advice to be sought.

In December, 1919 (aged 6), he was taken ill with an intense attack of vomiting, some blood accompanying the vomit on one occasion. The vomiting continued for several days, and about the fifth day he changed in colour and the abdomen swelled up. He was admitted to the Children's Hospital on account of ascites. During January and early February, 1920, he gradually

became worse; ascites increased, light jaundice was present and several attacks of epistaxis occurred, but there was no œdema in the legs or elsewhere.

On February 15, 1920, the abdomen was tapped and eighty ounces (over two litres) of fluid were removed. The liver could then be felt reaching to about one inch (2·5 cm.) below the costal margin; its edge was hard and nodular. The spleen was not palpably enlarged.

On March 3, 1920, he was discharged from the Children's Hospital, as he had developed pertussis. From this stage onwards his mother thinks that he was never well, though the ascites never recurred; gradually he developed further symptoms which his mother describes as "nervous debility," viz., he seemed to be getting stupid, dazed and drowsy, and she thought his memory was bad. He was readmitted to the Children's Hospital later in 1920, but no obvious signs of nervous disease could be then discovered; it is noteworthy that at this stage constipation had replaced the tendency to diarrhœa.

According to his mother he remained, during 1921, in the state described in the previous paragraph. In February, 1922, he had influenza, and after this it was noticed for the first time that the right arm and leg were getting "stiff." Slight attacks of diarrhœa and of vomiting occurred between March and June, 1922, and the nervous symptoms gradually became more pronounced.

He was admitted to the Birmingham General Hospital as an in-patient on November 8, 1922, and remained under observation for eleven days. On his admission a slight fever was present, his temperature being 99·8° F., pulse 120, and respiration 28. This was apparently a febricula of the catarrhal type, and was accompanied by some herpes of the nose and lips; it cleared up in about six days, by which time the temperature was subnormal, the pulse 96 and respiration 24. The urine had a specific gravity of 1012, was alkaline with a phosphatic deposit, but contained no albumin or sugar.

He was an undersized boy, 9 years old, and weighed $45\frac{3}{4}$ lb. His main symptoms (as related by his mother) were pain in the back and in the right leg, and inability to stand. The pains were clearly of a minor character and ceased almost entirely when he lay in bed; after observation it was concluded that they were due to overstrain of muscles in attempting to get about.

He lay in bed quite placidly, usually with his mouth open; a slight smile of a somewhat fatuous type was the most constant facial expression. At times he would laugh or cry unrestrainedly, a minimal cause being required to produce either effect. A tendency to drooling was persistent. His replies to questions were intelligent, but were given in a slow, drawling monotone; he never volunteered a statement and never used two words when one would suffice. All movements, both voluntary or emotional, of his face, tongue and jaws were slow and deliberate; there was considerable overaction of the facial muscles in associated action, such as a maximal voluntary clenching of an object in his hands. When such a grip was achieved with his right (most affected) hand, he usually required to unlock the fingers with the assistance of his left hand before he could release the object held.

There was general weakness of a spastic type which was much more pro-

nounced on the right side. The right arm was as a rule held adducted to the side and slightly rotated inwards at the shoulder; the elbow was extended, the hand flexed on the forearm, and the fingers lightly flexed at all joints. The limb was never fully flaccid, and the slightest voluntary effort, whether involving this limb or any other portion of the musculature, tended to increase the rigidity as a whole. In their slowness of relaxation after a strong voluntary contraction, the muscles of the right arm resembled those of myotonia (Thomsen's disease). No voluntary movement of the arm was lost, but so slow and awkward were the movements that the limb was useless in conveying food or drink to his mouth. Passive movements at first called forth increasing rigidity, but if repeated rhythmically several times in succession a gradual diminution of resistance was noticed—though the normal degree of relaxation of muscle tone could never be reached.

The left upper extremity presented only a slight degree of disability of the same character as that above described. So little was it affected that a careful examination was necessary to bring out evidence of abnormal rigidity, and the slowness with which voluntary movements were performed might easily have been mistakenly considered to be temperamental.

The trunk muscles were not demonstrably abnormal, but the right lower extremity was affected in the same way and to about the same degree as the right arm. Rigidity, feebleness without total loss of any voluntary action, a tendency to increased rigidity with any voluntary effort, and the presence of rigidity which diminished after repeated passive movement, were as marked in the leg as in the arm. The position of rest was one of general extension, the limbs lying side by side with the knees extended and the feet and toes plantar-flexed. A tendency to contracture was already present at the ankle, and passive dorsiflexion of the foot was incomplete.

The left leg, though much less severely affected than the right, was more obviously involved than the left arm; no measurable degree of contracture had yet occurred.

Although the musculature as a whole was poorly developed there was no local wasting, and no movement was totally paralysed.

Whenever the patient's attention was distracted for more than a few seconds, there occurred slow, writhing, athetoid movements of his right hand and forearm, and occasionally of the whole upper extremity. If he became at all excited the lower extremity was also involved, slow movement occurring towards the equino-varus position of the foot with adduction at the hip. These movements could always be controlled by an effort of will, but tended to occur if his attention was distracted in any way. Thus a conversation which interested him, an effort at drinking or to demonstrate the power of his left arm, at once permitted the athetosis to become manifest in the right hand and forearm. No athetoid movement was ever observed during sleep.

He could walk without help, but only slowly. In doing so he stood upright, or with only a little forward flexion of his head or trunk, and with a barely perceptible rigidity of the lumbar spine. His left leg was advanced naturally,

but the right, held rigid at the knee and plantar-flexed at the ankle, was swung outwards (abducted at the hip) in order that the toes might clear the floor. When he put his weight upon his right leg, the heel barely reached the floor, and it was impossible for him to maintain his balance without assistance. It was noticed that during walking grimacing movements in the face and athetosis in the right hand commonly occurred.

Examination of the rest of the nervous system was mainly negative. The eye movements were normal, the pupils reacted well, and the optic discs showed no change. The deep reflexes in the right arm and leg were exaggerated, knee clonus and ankle clonus being occasionally obtained. The abdominal reflexes, superficial and deep, were normal. The plantar reflexes on both sides were of the flexor type.

Visceral organs.—The heart, arteries and lungs were normal to physical examination. The abdomen was not protuberant and no ascites was present. There was no jaundice or icteric tint in the conjunctivæ or elsewhere. The liver could be felt on deep inspiration; its edge, reaching at most about 2 cm. below the costal margin was obviously rounded and hard, but was not tender. The spleen could not be felt, and was of normal size to percussion. No dilated veins were present around the umbilicus, or were visible anywhere around the attachments of the diaphragm. No deposit of pigment was present in the membrane of Descemet.

Progress.—The patient left hospital without material change on November 30, 1922. He was re-admitted on March 19, 1923, with a history of rapid decline in physical capacity. Speech had become very notably worse, and whereas on his previous admission the condition was one mainly of right hemiplegia of the lenticular type, it was now obviously bilateral. His mother was of the opinion that he was also failing mentally.

At this stage his facial expression was one of vacuity; his mouth was more widely open than before, though he still breathed easily through his nose. Replies to questions of a simple character were intelligent where intelligible, but his articulation was so bad that it was only with difficulty that he could be understood. Vowels were fairly well pronounced, but the dental and labial consonants were impossible to him.

The right arm and leg were more affected than on his previous admission, weakness, rigidity, contracture and athetosis all being more pronounced. His left arm and leg were much worse, though still not so severely affected as the right limbs were three months earlier. He could still walk, but not without personal assistance. Athetoid movements were now present in his left hand and forearm. His right hand was very feeble and the myotonic character of the grip had disappeared. No change in his reflexes had occurred.

At no stage was any tremor of a to-and-fro character seen in this boy.

The Wassermann reaction of his blood was still negative.

In January, 1924, he was again in hospital for observation. Some further deterioration in his physical condition had occurred, but the only noticeable addition to his physical signs was the occasional presence of an extensor

plantar reflex on the right side. On January 10, in company with his two sisters, he was shown at the Neurological Section of the Royal Society of Medicine (see *Trans. Roy. Soc. Med.*, Neurol. Section, January, 1924).

On October 6, 1924, he was admitted to hospital for the last time. During the previous twenty-four hours his spasms had suddenly become much more intense and painful, and he complained of pain in the abdomen. On his admission it was at once evident that he had developed broncho-pneumonia for he was breathing quickly, his temperature was somewhat raised (99° F.), and he had many crepitations at the bases of his lungs. He remained mildly febrile for five days, and then the temperature rose to 104° F.; death ensued a few hours later (fig. 1).

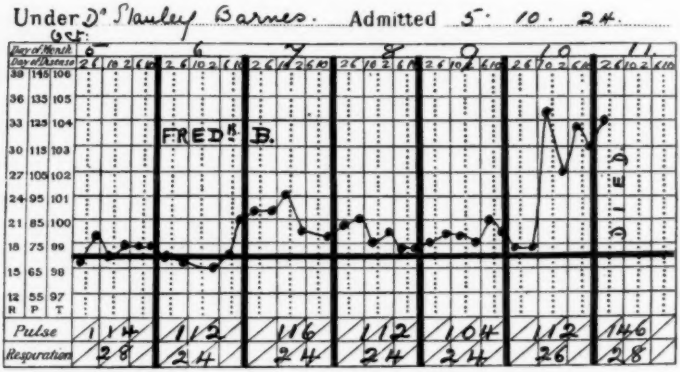


FIG. 1.—Case 1. Fredk. B. Temperature chart showing the character of the pyrexia present before death.

During this febrile period, a change had come over his general nervous condition. The rigidity was as pronounced as before, but now, and especially during the last few hours of his life when the temperature was considerably raised, he suffered greatly from a series of severe and generalized spasms, closely resembling those seen in tetanus. He lay in bed in an extended position, completely conscious but unable to articulate more than a mere gurgle; no word he attempted to utter was comprehensible. He sweated freely and his facial expression was one of pain and fright. His usual rigidity was now intensified by the spasms which occurred every fifteen seconds or so, and which subsided only partially after some five seconds. The trunk muscles were rigid throughout, so that any attempt at passive movement (which tended, as in tetanus, to increase his spasm) resulted in him being moved *en bloc* without any of the normal suppleness of the trunk and limbs. His neck was slightly flexed, all the muscles, and especially the sternomastoids, being in strong tonic contraction. His jaws were clenched in such a way that the

upper incisor teeth indented his lower lip, whilst the upper lip was everted and the angles of the mouth drawn down. The abdominal muscles were in such intense spasm that palpation of viscera was out of the question; the recti stood out sharply. Spontaneous movements of the legs occurred as part of the generalized spasms, the limbs being drawn up (flexed at the hip) and the feet strongly extended (plantar-flexed) on the legs. Similar spasms occurred in his arms, which were rigidly adducted to the trunk; a small degree of movement, from the fully extended to the slightly flexed postures, occurred at the elbow-joint during the spasms. The forearms were powerfully pronated, especially during the spasms, whilst spasm of the flexor carpi ulnaris caused the hand to be deviated at the wrist to the ulnar side. His hands were tightly clenched, more so during the spasms; even when partly relaxed it was not possible, passively or voluntarily, to extend his fingers or open his hands without causing general spasm and intense pain.

A tonic spasm, which never fully relaxed, caused flexion of the hips and knees. During the acme of his attacks the legs were lifted completely off the bed. Any attempt to straighten the limbs passively caused great distress; his back was arched (lordosis) and the head was retracted at the same time. Adductor spasm in the thighs caused the limbs to remain crossed throughout this period. His feet were in the equinovarus position, intensified during the spasm but never relaxing to the normal position; the toes were strongly flexed.

It was just possible to obtain knee-jerks and ankle-jerks between the spasms; the left plantar reflex was flexor and the right extensor in type.

His optic discs and pupil reflexes were normal. He had no pigmentation of Descemet's membrane. The ocular movements were normal in all respects. Swallowing was possible with difficulty; he was totally unable to masticate.

The spasms increased in severity on the evening of October 6, and caused him to make cries of pain. Breathing was more difficult. After a small dose of morphia he improved, the spasms nearly ceasing; rigidity was still strongly marked throughout. On October 9 the spasms recurred, being very severe in arms and legs; later the right side of the face was also involved; he sweated profusely during the attacks. He died at 4 a.m. on October 11, 1924.

Summary.—A normal boy with no unusual illness until 5 years old, began then to suffer from slight recurrent attacks of diarrhœa. When nearly 6 years old he developed an acute illness lasting for three months and gradually ending in apparently complete recovery. The symptoms of this illness were vomiting (at least once with blood in the vomit), a "change in colour" which was probably a light degree of jaundice, and ascites; some fever was present at this stage. After the first week there was increasing ascites, light jaundice and frequent epistaxis. The abdomen was tapped and 80 oz. of fluid were removed, liver then felt to be enlarged, hard and nodular; spleen was not enlarged. No recurrence of ascites, and no further gross signs of liver disease developed thereafter. No signs of nervous disease were noted by his relatives or by the doctors during his stay in the Children's Hospital at this period.

From this time he was never really well, and gradually changed in manner,

becoming "dazed and stupid." When re-admitted to hospital at the age of 6 years there were still no nervous signs. The boy was now constipated.

From now onwards evidence of progressive disease of the nervous system accumulated. By 1922, at the age of 9, the case was definitely diagnosed as one of progressive lenticular degeneration, on account of the type of paralysis, chiefly right-sided, which was present. His nervous signs increased gradually in severity though no signs attributable to liver disease were evident. A light attack of broncho-pneumonia in October, 1924, set up a blaze of nervous spasm of a tetanoid type, which proved fatal in a few days. He was 11 years old at death. He never showed any tremor.

Pathological Examination.

At the autopsy, conducted four hours after death, the body appeared emaciated to a considerable degree. There was no excess of fluid in any serous cavity, although the meninges were somewhat œdematous.

The brain was removed and preserved entire in formol-saline; no abnormality was noted in its appearance.

The liver weighed 600 grm. It was the seat of an advanced multilobular cirrhosis, and the liver surface projected in the form of numerous nodules which varied in size from that of a pin's head to that of a marble. These nodules were of a mottled-yellow colour and were separated one from another by bands of dense fibrous tissue.

The spleen, weighing 130 grm., possessed a rather thickened capsule and the pulp was firm and congested. The kidneys and pancreas were normal. The lungs showed an early broncho-pneumonia at the base; the apices were normal. The heart was normal.

Nervous system.—Horizontal sections, at intervals of 5 mm., were made through the cerebral hemispheres, beginning above at the level at which the lenticular nucleus first appeared. These sections revealed no macroscopic abnormality except in the lenticular and caudate nuclei. In the former region, however, there was a very definite shrinkage of the putamen, which was less than half its normal width and dark in colour, thus contrasting forcibly with the globus pallidus which showed no shrinkage and was of the usual colour (fig. 2). In consequence of the loss of nervous tissue in this region, the surface of the island of Reil was considerably depressed below its usual level. The convex curve of the outer border of the lenticular nucleus was lost and this margin was bowed inwards; the nervous substance was here very soft and during fixation splitting of the tissues had taken place between the external capsule and the putamen. It was obvious that the anterior part of the putamen had suffered less severely than the middle and posterior parts, for it was of lighter colour and of greater diameter than those other regions. By comparison the caudate nucleus was but slightly affected, but there was, nevertheless, some diminution of its bulk, and a distinct gap existed between its medial border and the opposite wall of the lateral ventricle.

The portions of the horizontal sections of one cerebral hemisphere con-

taining the basal ganglia were embedded in celloidin. Sections from these were stained by iron-alum hæmatoxylin and van Gieson's counterstain, by toluidin blue, by Loyez's hæmatoxylin method for myelinated fibres, and by ammonium sulphide with subsequent toning in a mixture of potassium ferricyanide and hydrochloric acid, for iron. From the basal ganglia of the opposite side of the brain, frozen sections were prepared and stained with alum hæmatoxylin and scharlach R., and with Victoria blue for fibrillar neuroglia (Anderson's modification of Anglade and Morel's method, *Journal of Pathology and Bacteriology*, 1923, **26**, p. 431). A piece of tissue containing the lenticular

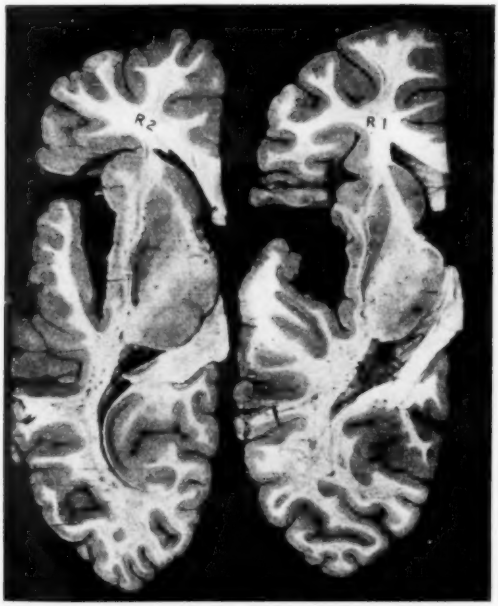


FIG. 2.—Two sections across the right cerebral hemisphere of Case 1, showing the marked shrinking and dark coloration of the putamen.

nucleus was placed in Flemming's fluid and sections from it stained by the Alzheimer fuchsin—light-green method. Parts of the cortex, brain-stem, cerebellum and spinal cord were also examined by the above methods.

Seen with a low magnification, attention was immediately arrested by the area of closely-packed nuclei and numerous capillaries which represented the putamen (fig. 4). This appearance was entirely confined to the outer division of the lenticular nucleus, except at one point where the morbid process had encroached to a very slight extent upon the adjacent part of the globus pallidus. The changes were somewhat more intense in the posterior part of

the putamen, while below, at the level where it fused with the head of the caudate nucleus, they were considerably less advanced. With appropriate staining, the radiating fibre tracts of the putamen were still clearly visible, though less evident than in a healthy brain.

With higher magnification, very few of the cells proved to be nerve-cells. The few neurons that remained presented various stages of degeneration and disintegration, of an advanced degree. The nuclei of those which survived were eccentric in position and distorted in shape. Often they were shrunken and considerably darker than normal, but some swollen and very pale forms were seen; in neither case was the nuclear membrane distinct. The nucleoli showed projections of their substance, becoming mulberry-shaped, and were

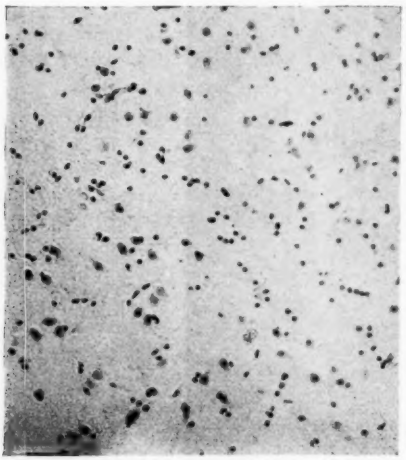


FIG. 3.—Low-power view of a normal putamen.

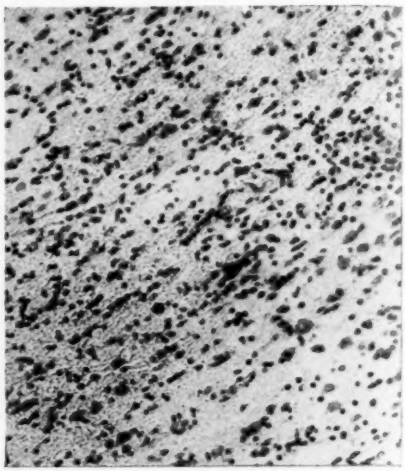


FIG. 4.—Low-power view of the putamen in Case 1, showing the enormous cellularity of this segment of the lenticular nucleus.

sometimes markedly eccentric in position. The protoplasm stained very irregularly with Nissl's method. Parts were intensely blue, while others stained scarcely at all or were distinctly granular; in no case was any normal Nissl substance visible. Many of the large cells contained small quantities of lipochrome pigment. The cell outlines were very irregular, satellitosis was of much more frequent occurrence than is usual in this region, and true neuronophagia was observed repeatedly. The most severely damaged cells were represented by pale and ragged masses of cytoplasm without a nucleus, surrounded and encroached upon by a mass of satellite cells. The paucity of the nerve-cells, especially of the large neurons, showed that many had already been completely destroyed.

The neuroglia showed both progressive and regressive changes. In addition

to being enormously increased in number, many of these cells were also considerably increased in size. The cell-bodies were often of the dimensions of a large nerve-cell, and were rounded or oval in shape without any very definite processes. The nuclei were also enlarged, but not always to a corresponding degree; in some the size of the nucleus was scarcely increased. Sometimes the nuclear enlargement was accompanied by poor staining of the chromatin, but usually a condition of marked hyperchromatosis and rarely of actual pyknosis was present. Masses of protoplasm containing two or three nuclei were seen here and there. Occasional neuroglial cells, of the type described by Alzheimer and known now as "Alzheimer cells," were seen (fig. 5). Their nuclei, varying in diameter from three to six times that of a normal neuroglial nucleus, were extraordinarily poor in chromatin which was repre-

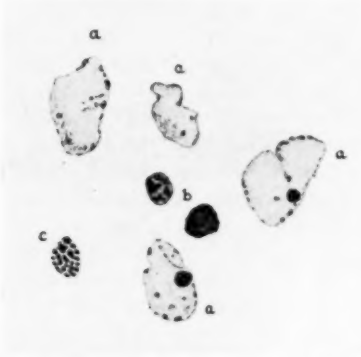


FIG. 5—Drawing illustrating the various types of neuroglial cells seen in Case 1. The large pale elements (a) represent the so-called Alzheimer cells. Two normal neuroglial nuclei are seen (b). At c is a nucleus showing hyperchromatosis.

sented by a few points of staining, usually along the nuclear membrane. Some were lobulated and in many the nuclear membrane was wrinkled. A definite nucleolus was often present. The cell-bodies were unstained by the Nissl method, but in fuchsin-light-green preparations showed rounded outlines without definite processes. No neuroglial fibres could be demonstrated, but this was attributed to faulty fixation.

In sections stained with Scharlach R., numerous granular corpuscles loaded with fatty products of degeneration, were seen, and curiously enough these were arranged in small foci. Such elements were also found around some of the vessels, while a few large globules of fat existed free in the tissues. Other inclusions of the neuroglial cells stained greenish by Nissl's method, or assumed a greyish tint, and around the vessels elements containing π-granules were of occasional occurrence. With fuchsin-light-green staining many of the glial cells were seen to possess fuchsinophil granules.

The increase in the number of capillary vessels could not be ascribed solely to the fact that shrinkage of the tissue had rendered more obvious those already present; it was quite evident that a considerable new formation of capillaries had accompanied the nervous degeneration. Along the course of the vessels were a number of degeneration bodies of lobulated or mulberry shape. They stained intensely blue-black with alum-hæmatoxylin and gave a well-marked iron reaction; in fuchsin-light-green preparations they coloured deeply with the fuchsin. Apart from that contained in these structures, the iron-content of the putamen was normal.

The other regions of the basal ganglia, though presenting some degree of neuronal degeneration, were by comparison with the putamen only slightly affected.

The contrast between the putamen and the globus pallidus was particularly striking. The enormous cellularity and vascular proliferation of the outer division of the lenticular nucleus ceased abruptly at the line of junction with the pallidum and under low magnification, except at one level where a very slight encroachment had occurred the impression of an almost normal globus pallidus was obtained. With a higher power, however, it was seen that none of its nerve-cells contained normally disposed Nissl bodies, and many stained irregularly and contained eccentric nuclei with mulberry-shaped nucleoli. A few were still more damaged and were undergoing neuronophagia. Many contained lipochrome pigment, though only in small amount. Although there was no gross increase of neuroglia, a certain number of hypertrophied glial cells were present, some of which showed hyperchromatosis of the nucleus; isolated Alzheimer cells were also seen. In the perivascular spaces were granular corpuscles containing fat and occasionally a cell with π-granules. Degeneration bodies of lobulated form were more numerous than in the putamen, and smaller spherical bodies of similar nature were quite common, especially in the anterior part of this region. Apart from the iron in these degeneration bodies, the iron-content of the globus pallidus was normal.

The changes in the caudate nucleus were of a somewhat more severe type and the large nerve-cells of this region had suffered considerably.

The thalamus, on the other hand, was nearly normal and but few of its neurons showed degenerative phenomena. The neuroglia, however, was somewhat hypertrophied. Many of the glial cells possessed a nucleus normal in size and tolerably rich in chromatin. The bodies of these cells were enlarged and attained diameters three times that of the nuclei; they stained faintly with toluidin blue, were rounded and without processes, and contained no inclusions.

The internal capsule showed no gross degeneration, and the fibres of the external capsule were also intact.

The nerve-cell changes in the cortex were again of a severe type. The Nissl substance was no longer present; the protoplasm was granular and irregular in its staining, some areas of the cell being quite pale while others were impregnated with a deeply staining substance. In still others the proto-

plasm had a meshlike appearance or actual vacuolation and honeycombing had occurred; such elements frequently showed neuronophagia, while satellitosis was a very common phenomenon around the less severely damaged neurons. The nuclei were eccentric, shrunken and darker than normal. The nucleoli, also often eccentric, had bud-like projections on their surface or were actually mulberry-shaped. In a few cases only a tattered remnant of protoplasm undergoing neuronophagia marked the site of a nerve-cell.

The neuroglial cells were probably somewhat more numerous than normal, though in the cortex the increase in their numbers was not a conspicuous feature. Many of the cells were hypertrophied and showed regressive changes in the nuclei, of the same nature as those described in the putamen; occasional Alzheimer cells were present. Granular corpuscles around some of the vessels,

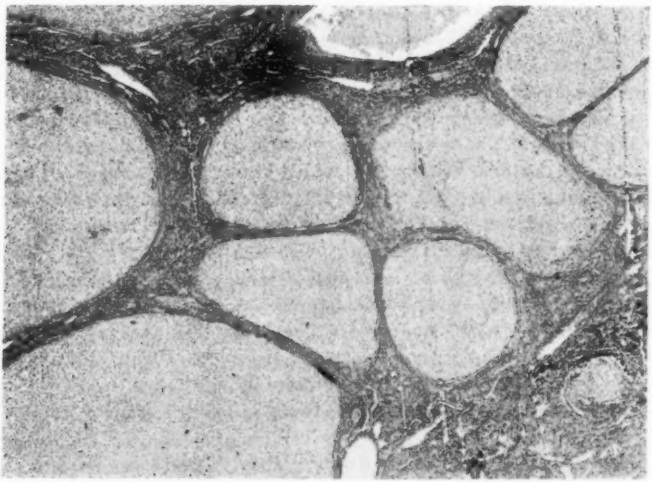


FIG. 6.—Low-power photograph of the liver in Case 1, showing a typical multilobular cirrhosis.

both here and in the subcortical white matter, and an occasional degeneration body, were further proofs of the occurrence of degeneration in the neighbourhood.

The brain-stem was normal.

The dentate nucleus and cerebellum showed changes of slight intensity comparable with those in the globus pallidus.

Liver.—It has been mentioned that the liver showed a condition of multilobular cirrhosis. Areas of liver tissue varying in diameter from 1 to 6 mm. were separated one from another by bands of greyish fibrous tissue which, for the most part, were less than 1 mm. in diameter, but around the portal veins attained a diameter of 3 to 5 mm. (fig. 6).

Microscopically the areas of liver tissue were seen to be composed of from one to four or more lobules. They were surrounded by fibrous tissue, the line of demarcation of which was, in most cases, quite sharp. In a few areas, however, there was evidence of invasion of the liver lobule in the shape of fine strands of fibrous tissue which penetrated for some distance from the periphery.

The majority of the liver-cells were affected by fatty changes and it was rare to find one completely free. The fat usually existed in the form of numerous fine granules and small droplets, though in some cells there were larger droplets almost entirely filling the cell. In some lobules the changes were equally marked throughout; in others there was a tendency for the peripheral parts to show the maximum incidence. At the periphery of the lobules some of the hepatic cells of larger size than normal contained two nuclei or a single very large nucleus.

The fibrous tissue was moderately cellular and vascular and contained a few areas of round-celled infiltration with occasional eosinophil cells.

There was, apparently, great proliferation of bile-ducts and numerous small ducts lay scattered through the fibrous tissue. At the margins of some of the lobules the liver-cells were separated into small groups and showed intermediate stages between the liver-cells proper and the cells lining the small bile-ducts. The lining epithelium of many of the bile-ducts had undergone fatty degeneration. Greenish-brown pigment was plentiful in those liver and bile-duct cells which showed fatty changes. It was not completely soluble in acetone, alcohol, xylol or a mixture of acid alcohol and ether. In frozen sections it stained metachromatically with neutral red. A part of this pigment resisted the action of 25 per cent. hydrochloric acid for several days, but none was seen after a week's immersion in hydrogen peroxide. It did not contain iron; in fact there was very little iron-containing substance in the liver, only occasional granules which gave an iron reaction being seen.

Case 2.—Phœbe B. She was first examined because her brother Frederick (Case 1) had been seen a few days previously. The history and an accurate record of her physical condition were first obtained in July, 1923, when she was aged 11.

As far as can be ascertained she was normal at birth, and suffered from no unusual illness during the first eight years of her life. When aged 8 she had a febrile illness which was called influenza (in February, 1920), and with it developed a transitory jaundice without any "dropsy" or swelling of the abdomen. This illness cleared up in a few days but ever since she had been subject to frequent attacks of vomiting, in more than one of which hæmatemesis had occurred. In February, 1922, her tonsils and adenoids were removed on account, her mother says, of a chronic nasal discharge. From this date the "sick turns" became more numerous, and were usually accompanied by feverishness; at this period, too, she first began to be "hysterical," and to exhibit clumsiness of her hand movements, awkwardness

of walking, and difficulty in speaking. A gradual increase of these nervous symptoms had been noticed, and they had now become so bad that school was out of the question.

On admission to hospital in July, 1923, when aged 11, she was noted as being exceptionally poorly nourished, and weighing only 45 lb. (fig. 7). As she lay in bed she was placid and as a rule without tremor or movement. The facial expression was rather vacuous, the mouth being kept open continuously; no abnormal facial twitches or tremors were present, and her smile was abnormal only in the tendency to be exaggerated. Her manner was somewhat facile and childish; speech was slurring and slow but easily intelligible, though she rarely volunteered any statement and was always sparing of her words. Her intelligence was fairly good, but it was obvious that she had not received the average education of a girl of her age.

The optic discs, pupil reflexes and eye movements were normal, no nystagmus being present. Movements of her face, jaw and tongue were all of normal power as far as they could be tested, but with all of them there was slowness and awkwardness in performing voluntary movement at command, though no tremor or athetotic movement was present. Swallowing occurred fairly easily, but a tendency to drooling was present. No sensory defect could be made out in the cranial nerve area.

There was a constant tendency to adduction and internal rotation of the arms. Her right arm was the more affected; it was held rigid, adducted at the shoulder, nearly fully extended at the elbow, sharply flexed and deviated a little to the ulnar side at the wrist, a little hyper-extended at the metacarpo-phalangeal, and flexed at the interphalangeal joints. The left arm showed only a slight tendency to adopt the same posture.

Hypertonia was present in the left arm, and reached a high grade in the right. Passive movement at the right elbow always increased the hypertonia, but, if flexion and extension were rhythmically repeated many times, the hypertonia tended to diminish slowly.

Contracture of some degree was already present in the hand, but by passive movement it was just possible to obtain full extension of fingers and wrist.

Both legs were rigid, the right more so than the left. The usual position of the right leg was adduction and nearly full extension, with some internal rotation at the hip, extension at the knee, and inversion of the foot into the equinovarus position at the ankle. On the right side definite contracture had occurred at the ankle-joint, but none was present on the left.

In standing the limbs tended to maintain the same positions as in lying down; in addition the head was bent slightly forward, there was a little forward curvature of the lumbar spine and a slight lateral curve of the vertebral column, concave to the right side. The photograph (fig. 7), taken July, 1923, shows this attitude very well, and as the exposure was nearly two seconds, it shows that no perceptible tremor was present at this stage.

She could walk without assistance, but the right leg was swung outwards

rigidly and cleared the ground with difficulty owing to the failure of flexion of the ankle.

No sensory defect could be made out anywhere, and no spontaneous pain was present—after efforts to use the hand or foot there was occasionally some pain, probably caused by strain on the muscles and tendons.

All reflexes including the abdominal and plantar reflexes were normal.

FIG. 7.—Case 2. Phoebe B. July, 1923. The photograph is taken with a time exposure of about two seconds, showing that no movement took place during that time. The contractured position of the right hand and foot are shown, together with the usual attitude in standing; the degree of emaciation is well shown.

Occasionally during her stay in hospital some spontaneous movements were seen in the right upper extremity. They resembled athetosis more than chorea or tremor: a slow, writhing contraction of the forearm and finger muscles, with increased rotation inwards of the whole limb at the shoulder-joint, caused the hand to be so inverted that the palm faced outwards and nearly forwards. This movement required some two to three seconds to reach its maximum, when the spasm gradually relaxed and the arm and hand reverted to their normal position. At times, during the access of the spasm, a to-and-fro flexor

tremor of the wrist was seen, the rate of oscillation being three to four to-and-fro movements per second. Athetoid movements were occasionally seen in the right lower extremity, the spasm being in the direction of increased deformity (rotation inwards at the hip and ankle, with some flexion of ankle, foot and toes)—the athetosis here was not accompanied by any tremor. At this stage she always appeared to be able to control these movements by focusing her attention upon them, but they tended to occur at once if her attention was distracted by conversation, and particularly if she was asked to perform a powerful or difficult movement with her left hand. At such times the usual grimace expressive of determination made by a normal patient was exaggerated but not grossly so.

The liver could be felt, its edge being hard and rounded and reaching from 2 to 4 cm. below the costal margin. There was no ascites or jaundice. The spleen edge was also palpable and was harder than normal.

A persistent nasal discharge was present, purulent and occasionally flecked with blood. The other organs appeared to be normal.

FIG. 8.—Case 2, August, 1924. The hand is being held horizontally by voluntary power, and shows tremor more particularly of the middle finger; a greater degree of contracture is present than in the previous photograph. Time exposure, two seconds.

The child remained in hospital for a period of four weeks, during which she slowly became worse in her nervous symptoms. The temperature throughout this period was irregular, ranging from 97° F. to 99·8° F. The urine was normal and there was neither constipation nor diarrhœa. Appetite was poor and lassitude was pronounced.

An effort was made to determine the liver function, the lævulose test being used. The blood-sugar before administration was 0·21 per cent.; half an hour afterwards 0·22 per cent., and in one and a half hours it was 0·26 per cent.

The story from this stage onwards is one of slow but persistent deterioration, with occasional periods of remission in which she at least held her own and occasionally seemed to improve. She always seemed to be worse when her temperature was irregularly high, and during the remissions there was always apyrexia.

On March 10, 1924, the lævulose test gave figures (corresponding to the above) of 0·09 per cent., 0·10 per cent. and 0·105 per cent.; at this date neither

liver nor spleen could be felt. By August 25, 1924, she was much worse and was approaching a bedridden stage. This time she remained in hospital for a period of twelve days, the temperature being mildly pyrexial until the end of her stay, when her condition again improved. She was now only just able to get about with much personal assistance; the hypertonia was much increased on the left side, and so severe in the right arm and leg as to make these limbs nearly useless for feeding or walking. The muscles generally were much wasted, and in the right hand (fig. 8) it was noticed that both athetosis and tremor were present, the latter only during attempts at voluntary movement or during the progress of an athetoid spasm. Her facial expression had become more vacant.

For the first time it was now noted that an extensor plantar reflex could occasionally be obtained on the right side; it was, however, of the light variety and repeated stimuli during non-athetoid periods soon brought out a flexor response once more.

In March, 1925, she had a fresh outburst of pyrexia (the temperature rising at times to 103° F.) which was believed to be due to influenza, as it was epidemic at this period. After ten days the temperature subsided to normal, and a further remission occurred. Re-examined then it was clear that her physical capacity was less than on the previous examination. She could now no longer stand nor use either hand for feeding herself; swallowing was a slow and difficult process and drooling was persistent; there was no incontinence. The expression of the face was now usually one of pleasurable vacuity and the mouth was much more widely open than before. Although uncontrollable laughing and crying were not present, both her smile and her expression of distress were abnormally slow to develop and more easily called forth than in the normal child, and there was always an element of the grotesque in each.

Some contracture was now present in her arms (figs. 9, 10 and 11), both of which were hypertonic and held to the sides flexed at the elbow. No tremor was present when at rest, but an attempt at gripping with either hand caused tremor of a flexion-extension excursion to occur at the wrist-joint, particularly of the wrist which was *not* being voluntarily put into action. Such tremor as there was during this action was far less rhythmical and more jerky than is seen in most cases of this disease; athetoid movement had now largely ceased, and passive movement, which always increased her rigidity, was so painful that no prolonged tests could be made.

The legs had deteriorated to an equal degree as the arms. They were thin though not locally wasted; hypertonia and occasionally some tremor was present, but no athetosis or choreiform movements were now seen.

The trunk muscles shared in the general rigidity, but the abdominal reflexes were present. Some kyphosis had developed, and she could no longer sit up in bed without support.

Her mental condition was clear, but of a childish type. She obviously understood simple questions, but the dysarthria was so gross that her mother or the ward sister were alone able to interpret the reply. The act of swallowing was difficult, fluids and some semi-fluids alone being taken.

The plantar reflexes were again flexor in type, and the other reflexes were unchanged. The liver was not palpable throughout her stay in hospital (twelve weeks).

At this stage various efforts were made by my house physician (Dr. A. J. Davies), and our clinical pathologist (Dr. W. T. Hillier), to determine the liver efficiency; all of them gave normal results. No urobilin or urobilinogen was found in the urine, and the ammonia coefficient was 1·5 per cent. A test meal was given to determine whether any acid was present in the gastric juice; it showed that hydrochloric acid was present in normal amount. It should be

FIG. 9.—Case 2, December 1924. She was unable to sit upright without personal assistance, and some tremor of the head had developed. The left hand shows contracture now.

stated that these tests were all carried out after an apyrexial period of six weeks.

Since this period there has been little change, and no further decline in health was noted in June, 1925. She was re-examined in July, 1925, and no substantial change in her nervous condition was observed, with the exception that the flexion-extension tremor of the right wrist was more pronounced, though it occurred only when active voluntary movement was attempted, either by that limb or by any other. No athetosis or chorea was present.

This opportunity was taken to have her carefully examined for the presence or absence of the Kayser-Fleischer line. Nothing had been seen by the use

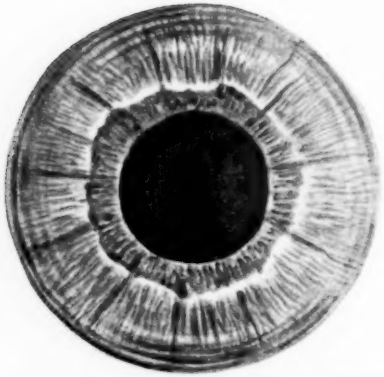
of ordinary methods, but Mr. Harrison Butler kindly undertook an examination by the slit-lamp. This was accomplished with great difficulty owing to the child's contractures and the difficulty of keeping her still in the necessary position. Mr. Butler reports as follows :—

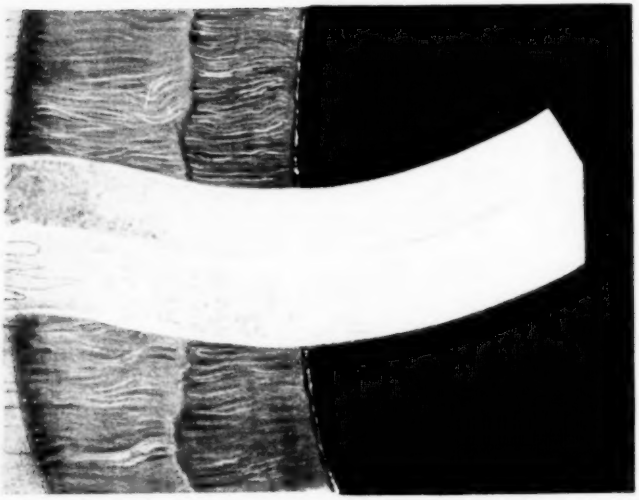
FIG. 10.—Case 2, December, 1924.

FIG. 11.—Case 2, December, 1924. Shows the decubitus and the absence of tremor when at rest.

"The girl Phœbe showed the Kayser-Fleischer ring in the right eye but not in the left.

"The slit-lamp examination was very difficult on account of the general





The upper drawing represents the anterior aspect of the eye as seen with the loupe, and shows the delicate golden glow upon the lower portion of the iris.

The lower coloured drawing shows the Kayser-Fleischer ring as seen with the slit-lamp. The beam of the lamp in passing through the cornea illuminates a sinuous block of cornea generally called the corneal "prism," with a curve mainly convex but reversed at the limbus. The anterior or epithelial surface is to the left, and is normal. On the right is the posterior or endothelial surface, which shows a granular pigmentation, brown above (near the limbus) and gradually becoming yellow and fading away towards the centre of the cornea, being no longer perceptible just central to the line where the cornea is seen crossing the inner edge of the iris. The corneal nerves shown on the prism are normal in aspect and are not increased in number.—(T. HARRISON BUTLER.)

condition of the child, and because there was at times considerable movement of the eyes. It is therefore possible that there may be traces of the ring in the left eye, but I did not see them.

"Examined with the focal illumination of a half-watt lamp and the simple loupe magnifying about six times, there was no sign of the ring, but I noted that when light was thrown obliquely from above upon the iris, so that the light passed through a considerable thickness of the cornea at its lowest periphery, the lower part of the iris had the appearance as though the evening sun were shining upon it; there was a most unmistakable golden glow. But for the difficulty in the examination I have no doubt that I should have seen the actual ring with the loupe.

"Examination with the slit-lamp and the corneal microscope under a magnification of 23 showed that the posterior surface of the cornea was pigmented above and below, but I was not able to see any pigmentation at the lateral aspects. Again the difficulty of the examination may have prevented me from discovering the pigment in this situation. The pigment was yellow towards the centre of the cornea, golden-brown at the periphery. The extent of the ring was from the periphery to about one-fifth of the diameter inwards. The appearance seen was exactly that described by Kayser and others. The corneal endothelial cells were well developed and normal. The Hasal-Henle 'craters' were present as in the normal cornea."

In view of the rarity of the zone being observed in Wilson's disease, and of its appearance being so little known in this country, Mr. Harrison Butler has kindly made two coloured drawings of the slit-lamp arrearance in this case (see Plate).

Summary.—A normal girl in the first eight years of her life. She then had a febrile illness with transitory jaundice. During the next three years she suffered from repeated attacks of vomiting, in some of which hæmatemesis occurred. At the age of 10 nervous symptoms began to be manifest. At the age of 11 she was admitted to hospital with definite nervous disease; at this time the liver was enlarged to palpation and a slight febrile reaction was present. Nine months later the liver was no longer palpable but the nervous condition was much worse. When 13 years old a fresh outburst of pyrexia occurred; she had now reached a bedridden stage. During the last three months no material change has taken place. Corneal pigmentation is present in the right eye.

Case 3.—Elsie B. *History.*—This member of the B. family was examined with the others early in 1923 by Dr. Cochrane. At that time she was 7 years old and showed no evidence of disease of any sort, the nervous system and liver being particularly examined.

During the latter half of 1923 she began to suffer from intermittent "sick turns" in which she would shiver, vomit and complain of headache for periods of a few hours; the attacks occurred at intervals of a month and were looked upon as "bilious attacks" (migraine). An attack of this type began on December 24, 1924, without obvious cause, and on this occasion was more

severe and prolonged, and accompanied by fever. On December 25 she was noticed to be jaundiced; she complained now of abdominal pain and noises in the head and still vomited. On December 26 the abdomen began to swell, and this swelling increased though the vomiting was ceasing. On December 31 a sharp attack of pain in the left side was again accompanied by vomiting, the rejected fluid being of a dark yellow colour with a sour odour. The pain extended from the left costal margin completely across the abdomen, and was intensified by taking food. Neither diarrhœa nor constipation was present during the acute illness.

FIG 12.—Case 3. Elsie B., January, 1925. Pre-nervous stage, with ascites.

State on admission (*December*, 1924).—She was a girl of average development for her age (8) and was neither unduly fat nor thin; there was no indication of wasting (fig. 12). She lay placidly in bed with no evidence of pain. The conjunctivæ were definitely yellow, and an icteric tint of a light type was universal.

The teeth as a whole were good, one tooth only being carious; the gums were free from pyorrhœa. The tongue was clean and not furred, and the fauces were normal. The abdomen was uniformly distended with a moderate

amount of free fluid (estimated as about 40 oz.) which was sufficient in quantity to prevent any accurate examination of the viscera; it was, however, possible to feel the spleen about 1½ in. (4 cm.) below the costal margin during deep inspiration, and by "dipping" to make out that the liver extended to about an inch below the ribs. The upper border of the liver was determined by percussion to lie at the level of the seventh rib in the mid-axillary line. There was no pain on light palpation of the abdomen.

There was no evidence of disease in the heart or lungs. The blood-pressures were 118 (systolic) and 60 (diastolic). The urine was of a dark-reddish colour, gave the reaction for bile pigment, had a gravity of 1030 and contained a light cloud of albumin, but no sugar. There was no deposit, and no casts or crystals were found with the microscope.

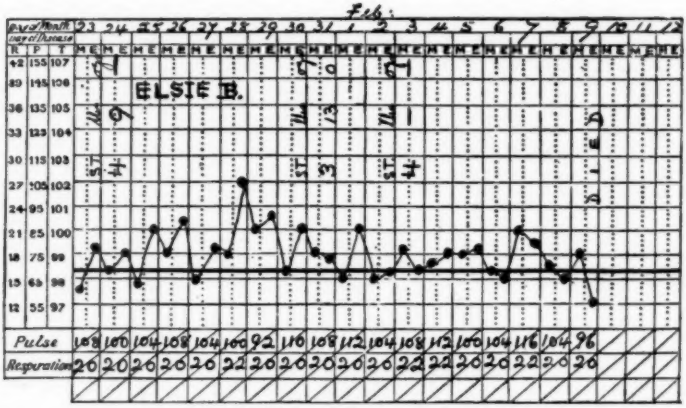


FIG 13. Case 3.—Temperature chart showing the irregular pyrexia present.

The nervous system was normal throughout. No record was made of the presence or absence of pigment in Descemet's membrane.

A blood-count showed: red cells 4,100,000, white cells 32,000, hæmoglobin 60 per cent., colour index 0·75.

This was her condition when on January 10, 1924, she was shown at the Neurological Section in London, together with her brother and sister.

Progress.—From the first day of her admission, some degree of fever had been present. As a rule this was of moderate degree, ranging from 98° to 100° F. during the twenty-four hours, and only occasionally reaching 102° F. The highest temperature was usually reached in the evening. No evidence of disease elsewhere than in the liver could be found as a cause of the fever, which, despite minor fluctuations, remained of about the same degree throughout. The ascites, after apparently subsiding a little, increased rapidly about January 24, and on January 27 some œdema of the ankles and cardiac distress were present.

On January 28 the abdomen was tapped and 140 oz. (four litres) of fluid were removed. During the next few days much vomiting and prostration occurred. By February 6 a large ascites had again accumulated, and the superficial abdominal veins were engorged, but no œdema of the legs was present. A second paracentesis on February 9 removed 80 oz. of straw-coloured liquid, but she was very much collapsed at the end of the operation and died a few hours later.

During her stay in hospital a lævulose test showed very severe impairment of liver function. The percentage of sugar in the blood before administration of lævulose was only 0·0625 per cent.; but after 30 grm. of lævulose had been taken by the mouth, the percentage rose to 0·26 per cent. in one hour and to 0·3 per cent. in two hours.

Tests for fragility of the red cells were also carried out by Dr. Hillier; complete hæmolysis occurred in 0·25 per cent. sodium chloride solution, incomplete in 0·3 per cent.; a trace in 0·45 per cent. and none in 0·5 per cent. This result was interpreted as being within normal range.

Summary.—Elsie B., aged 8, was normal till she reached the age of 7½. Then began to suffer from attacks of "migraine" lasting one day or less and occurring at intervals of about one month. A severe "migrainous attack" on December 24, 1923, passed on to a condition which was considered to be acute hepatitis, in which vomiting, jaundice and ascites were prominent symptoms. No signs of nervous disease. Death after seven weeks' illness. Evidence of severe loss of metabolic efficiency of the liver was obtained, but the fragility of the red cells was normal a few days before death.

Pathological Examination.

The autopsy was conducted seven hours after death.

The brain showed no abnormality except that there was, perhaps, some widening of the perivascular spaces in the putamen. Otherwise there was no evidence of shrinkage of the tissues in this region (fig. 14).

The peritoneum contained about three pints of bile-stained serous fluid.

The liver weighed 600 grm. and was of a mottled-yellow colour; the surface was studded with small nodules (fig. 15). On section of the organ areas of liver tissue varying in diameter from 1 to 4 mm. were seen to be separated by bands of pinkish-grey connective tissue which varied in width from 1 to 3 mm. The liver substance was markedly fatty and distinctly jaundiced.

The spleen was 200 grm. in weight, firm in consistence and deeply congested. There was, however, no notable increase in connective tissue.

The kidneys, which weighed 120 and 90 grm. respectively, were somewhat fatty.

The alimentary tract was congested and œdematous, but there was no evidence of ulceration or inflammation.

Nervous system.—The brain was treated in the same manner as in Case 1.

Microscopically certain regions of the brain showed degenerative processes

FIG. 14.—Cross-sections of the basal ganglia of Case 3. There is no obvious abnormality of the lenticular nuclei.

FIG. 15.—Photograph of the liver in Case 3, showing the nodular surface of the organ.

in the nerve-cells. These were definitely more advanced, and of a very much more severe type in the putamen of the lenticular nucleus than elsewhere.

In that region the large nerve-cells were decreased in number as compared with those of a normal child of the same age. The remainder stained diffusely or irregularly; in the latter case parts of the protoplasm were intensely basophil, while others had become completely decolorized. No normally arranged Nissl substance was present. The cell margins were very ragged, the nuclei eccentric and shrunken, and the nuclear membranes indistinct. Satellitosis was very common and neuronophagia of the more severely damaged neurons was in progress. The small nerve-cells had undergone somewhat similar changes; no longer of sharp and regular contour, the clear protoplasm had become granular and woolly in appearance and the nuclei were degenerated in the manner already described.

There was no noticeable increase in the numbers of neuroglial cells, but there was a distinct tendency to hypertrophy of those present; this was never

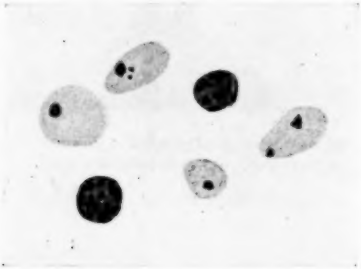


FIG. 16.—Drawing depicting an unusual type of neuroglial cells met with in Case 3, the nuclei of which are extremely poor in chromatin. Two normal neuroglial cells are shown for comparison.

of more than moderate degree. In addition a peculiar type of neuroglial cell was of very frequent occurrence and was derived, apparently, from that type which usually possesses a nucleus poor in chromatin, since various stages in the development of these cells were seen (fig. 16). The outlines of the cell body were not visible as were those of the elements with darker nuclei. The nuclei tended to swell and at the same time to become paler, with all their chromatin collected into one or two intensely staining granules. The nuclear membrane became increasingly indistinct and finally, when the nucleus had attained a diameter of two or three times the normal, the membrane disappeared, leaving a granule or granules representing the aggregated chromatin lying free in the tissues.

With the exception of a few granules of lipoid in the capillary endothelium there were no collections of Scharlach-staining products of degeneration in the putamen, but in the external capsule a few of the Virchow-Robin spaces contained granular corpuscles loaded with lipoid.

The vessels showed plugging of the lumina with bacteria, a condition present in most regions of the brain, and obviously to be regarded as merely a terminal event. Otherwise they presented no abnormality. Mulberry-shaped degeneration bodies were present here as in the preceding case and gave the same reactions. Apart from the iron contained in these, the iron-content of the putamen was normal.

In the globus pallidus the condition of the nerve-cells was very different. Here, the majority of the neurons were very well preserved, possessing normally disposed Nissl substance, and only a few showed early degenerative changes. Mulberry bodies were present; otherwise the iron-content of this segment of the lenticular nucleus was normal. In the caudate nucleus a

FIG. 17.—Low-power view of the liver in Case 3. The fibrous tissue is more diffuse than in Case 1, and invasion of the liver lobules is a conspicuous feature.

rather more advanced degeneration of the large nerve-cells was observed which, however, was but slight in comparison with that in progress in the putamen. The thalamic neurons were normal. In all these regions the pale neuroglial nuclei already described were encountered, though their numbers were not very great.

In Weigert-Pal preparations there was no evident degeneration in the internal or external capsules, or indeed in any fibre systems except the radiating fibre tracts of the putamen which were somewhat paler than normal.

In the cortex some of the nerve-cells were slightly swollen, with a tendency to mesh formation or actual vacuolation of the protoplasm and irregular staining with toluidin blue. Their outlines were often ragged; satellitosis was common and neuronophagia occasionally observed. The nuclei were displaced from the

centre of the cell and were darker than normal. Sometimes, however, the whole cell, including the nucleus, was stained feebly and was almost phantom-like. Nevertheless, the changes here did not approximate in intensity to those in the putamen. The neuroglia presented changes similar to those in the putamen, the pale nuclei already described being fairly numerous in the cortex. In sections stained with Scharlach R. granular corpuscles with fatty contents were seen around some of the subcortical vessels and fat was also present here and there in the capillary endothelium.

The brain-stem, cerebellum and spinal cord were normal.

The liver appeared very different from that in the preceding case, and the impression given was of a healing subacute yellow atrophy rather than of an ordinary cirrhosis (fig. 17).

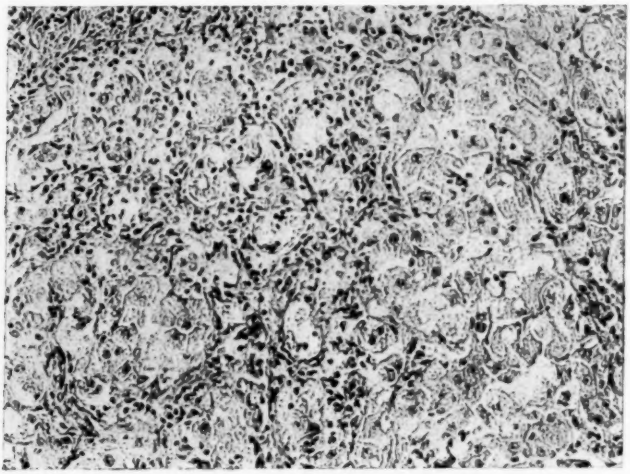


FIG. 18.—High-power view of the liver in Case 3. The liver cells are arranged in small groups separated by strands of cellular connective tissue.

A few comparatively normal lobules, showing only slight fatty change, were seen, but the majority were much more severely damaged; when stained with Scharlach R., these appeared as bright orange-red patches, for nearly every cell contained a larger or smaller amount of fat in the form of fine, medium-sized or large droplets. Some cells consisted of little else than a large drop of fat surrounded by the thinnest possible rim of protoplasm containing a much compressed nucleus. Generally speaking the most intense changes were found in the central parts of the lobules, which in one or two instances seemed to be on the verge of disintegration. But very occasionally the centre of the lobule was comparatively normal, and there was a zone of fatty degeneration at the periphery. Often there were, in the peripheral parts

of the lobule, a few cells larger than normal with two nuclei or one nucleus several times the normal size.

In other areas liver tissue existed without definite lobular structure, the cells lying in groups of two or three separated by thin strands of fibrous tissue. Many of these were intensely fatty and probably represented the remains of an extensively damaged lobule. Others, again, were shrunken considerably; such cells existed both in isolated groups and around some of the liver lobules. Altogether less than half of the liver substance was arranged in lobular form, the remainder consisting of scattered groups of cells and fibrous tissue (fig 18).

The fibrous tissue was very vascular and fairly cellular, and was infiltrated in places with round cells, eosinophil cells and plasma cells. Numerous small bile-ducts were present and a series of intermediate stages between the liver cells at the periphery of the lobules and the cells of these ducts could be traced. Many of the small ducts were filled with a bright apple-green homogeneous substance which could also be followed between the liver-cells in the lobules.

After removal of the fat by acetone, a greenish-brown pigment remained in some of the liver-cells; it did not react to iron stains and possessed similar properties to that described in the previous case.

Case 4.—Daniel B. *Previous history.*—In 1923, when the first member of this family was definitely found to be a subject of lenticular disease, my then house physician (Dr. Cochrane) kindly visited the patient's home and examined all the other children. Amongst them was Daniel (then aged 6); the only abnormality found on that occasion was that the liver was palpable below the costal margin, and that it was too hard. The spleen was not palpably enlarged.

About January, 1924, when 7½ years of age, he had an attack of vomiting which lasted several days; during this time his mother says he "went a nasty colour," which was not exactly yellow but had a "suggestion of a pale yellowish tinge." He was feverish, and for a few days the fæces were pale yellow and "frothy, like barm." He recovered from this attack in a few days, and was reasonably well thereafter till December, 1924. A week before Christmas, a severe attack of vomiting occurred; he vomited about every hour for two days, and had diarrhœa with fæces of the same type as in his previous attack. No hæmatemesis occurred. His only pain was in the mid-axillary line near the costal margin on the right side. After the first two days the vomiting ceased, but nausea was continuous and he lost some weight.

His mother states that a year ago (before his first vomiting attack) his mental condition was normal for a boy of his age, but that ever since he seems to have been more backward than he should; he was constantly in trouble at school for his incapacity to learn, and if sent by his parents on an errand was liable to return without having accomplished his mission, by reason of failure of memory. His mother has also noticed that during the last month—

(1) "He dashes about in an unrestrained manner, climbing everywhere."

(2) "He laughs like a nigger," presumably meaning that his laugh has changed in character, and is roused by trivialities; occasionally it occurs without any obvious reason.

(3) Any remonstrance from his parents causes unrestrained fits of crying.

(4) He cannot sit still in a chair; he fidgets more than he used to do.

(5) He makes fanciful but untrue statements, as for instance "I have just seen a man run over outside."

(6) He has become intensely inquisitive, wanting to touch, manipulate and investigate anything that meets his eye. He is destructive to books, papers and toys. This is a new trait in his character.

(7) His sleep is disturbed. By night he tosses about, reducing the bed clothing to a state of chaos. He is always restless by day, when it is impossible to make him either rest or sleep.

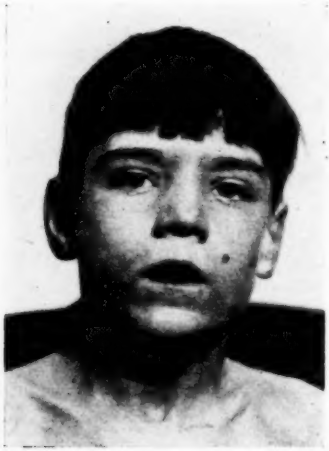


FIG. 19.—Case 4, Daniel B. Facial appearance in the pre-nervous stage.

There has been no difficulty with getting him to take food.

It was at this stage that he was brought to the General Hospital, and on account of the family history he was admitted on January 6, 1925.

State on admission.—He was a rather poorly nourished boy, aged 8 years, and weighed only fifty-two pounds. The general aspect of the face was somewhat vacuous (fig. 19). He was not shy and responded reasonably to simple questions, speech being normal in character but rather slow. It was, however, obvious that his intelligence was not up to the average standard of a boy of his age. His gait was within the limits of the normal; he walked freely and easily without assistance, but with a suggestion of self-consciousness which may have been due to very early nervous damage. His mother thought he was going "in

the same direction as his brother and sister," so far as gait was concerned; but she was probably hypercritical, and had become pessimistic about her children. No defect could be made out in his musculature, nor in his capacity for putting his muscles into action. The associated movement of the face when attempting a powerful grip was perhaps a little more expressive of a leer or sneer than of determination, but was nevertheless well within the limits of normal variation in expression. No tremor, athetosis, muscular spasm or rigidity was present. No pigmentation of Descemet's membrane was seen by a naked-eye examination with good illumination; as however his iris was very dark, a minor degree of pigmentation might have been present without being appreciated.

An examination of the stomach contents was made, and the degree of acidity present in the fasting juice was 0·04 per cent. for hydrochloric acid and 0·14 per cent. for total acids. He took the tube with difficulty and it was impossible to plot out a fractional curve as he vomited the œsophageal tube within a few minutes.

The liver was definitely enlarged downwards, the edge being felt nearly two inches below the costal margin during deep inspiration, and being much harder than normal.

Van den Bergh's reaction was performed on one occasion; the serum gave no direct reaction and the indirect reaction was feeble (Dr. W. T. Hillier's observation). The blood-sugar, also estimated by Dr. Hillier, gave a percentage of 0·12; after the administration of lævulose the two estimations were after one half hour 0·10 per cent., and after one hour 0·12 per cent.

On July 10, 1925, he was examined by the slit-lamp in order to determine whether any Kayser-Fleischer line was present. Mr. Harrison Butler sent me a report to the effect that he showed no sign of corneal pigmentation when examined either with the loupe or with the slit-lamp and corneal microscope.

Summary.—Examined on account of the family history in 1923, he appeared to be a normal boy of 6 years of age, with the exception that the liver was rather large and hard.

At age $7\frac{1}{2}$, a severe attack of vomiting lasting several days, with slight fever, diarrhœa, altered colour of fæces, and an altered colour of the tissues which may have been icteric. Recovery was apparently complete.

At the age of 8, recurrence of the above symptoms in acute form, with slight fever. During examination in hospital, no evidence of failure of metabolic activity of the liver could be determined by the Van den Bergh or by the lævulose test, but the liver was large and hard.

After recovery from the acute attack, examination of the nervous system was negative, although his mother (an acute but pessimistic observer) thought that he had changed during the last twelve months for the worse in character and habits, and that his walking was deteriorating.

Clinical Symptoms.

The nervous symptoms first described by Wilson [45] in progressive lenticular degeneration constitute a group which he considered to be characteristic of lenticular damage. Essentially they were "generalized tremor, dysarthria and dysphagia, muscular rigidity and hypertonicity, emaciation, spasmodic contractions, contractures, emotionalism. There are also certain mental symptoms . . . and a certain facility or docility . . . The mental symptoms may be very slight and are sometimes absent." In another portion of his monograph, he sums up the clinical symptoms thus:—

"In pure, uncomplicated, bilateral lesions of the lenticular nucleus, and more generally of the corpus striatum, provided they are of sufficient size and of adequate duration, the clinical symptoms are bilateral involuntary movements, practically always of the tremor variety . . ." The reservation implied in the last clause evidently referred to the cases of Gowers [13, 14], Ormerod [28], and Homen [18], in all of which tonic and clonic spasms rather than tremors were the outstanding features of muscular action. In Gowers' first case the description as originally given by him in his "Diseases of the Nervous System" [13] under the title "Tetanoid chorea" is worth quoting in full, for Gowers, an unusually acute clinical observer, gives a very graphic picture of the movements in this case. The description is as follows:—

"A case was recently under my care that presented symptoms intermediate between those of chorea and of tetany. The disease was fatal and no lesion was found after death. The patient was a boy, aged 10. A brother was said to have died from some affection similar to that from which this boy was suffering. There was a history of three other relations having suffered from maladies resembling chorea. In the patient the symptoms commenced gradually, seven months before death. They consisted of tonic spasm, which was continuous, and varied by paroxymal attacks of a similar, but more intense, spasm. The face was involved on both sides, so as to cause a constant peculiar smile. The tongue was pressed back against the palate in such a manner as to impede swallowing and prevent speech. The arms were extended, pronated and rotated inwards, so as to bring the back of the forearm outwards, whilst the fingers were generally slightly flexed at all joints, but at times were extended and slowly moved in the irregular way characteristic of athetosis. The legs were extended at all the joints, the feet being overextended in talipes equinovarus, and the toes were flexed. At times the spasm at the hip became flexor, so that the

extended legs were raised off the bed. The muscles of the trunk were also involved in the spasm. At first the left side was the more severely affected, but afterwards the spasm became equal on the two sides. The electric irritability of the muscles was normal and there was no mechanical excitability of the nerves. There was considerable pyrexia during the more severe stages of the disease. The boy steadily emaciated, and died from exhaustion. The whole central nervous system appeared normal to the naked eye, and no distinct morbid appearances could be discovered on microscopical examination. I have not been able to find a description of any quite similar case."

The case was later republished by Gowers [14], still under the title of "Tetanoid chorea," and with the addition of a second case, sister to the first one. In the latter, the symptoms are again described as being chiefly spasmodic or tetanoid, but occasionally tremor of the tongue and at the hips and knees occurred.

Tremor.—No one reading the above account (of Gowers' Case 1) can fail to be struck by the close resemblance of the symptoms to those which have been described in our Case 1. Spasm of a type which gave rise to writhing movement, involving a whole limb or even the whole body, was characteristic of both cases; in neither was there any movement which could justly be called tremor. But in his Case 2, as in our Case 2, occasional tremors were seen in addition to the tetanoid spasms; it is a point of some interest that the cases showing such tremors were both girls, in whom the course of the disease was of longer duration than in the cases of their respective brothers.

If therefore we accept Gowers' second case and our own Case 2 as being correctly grouped with Wilson's own cases, clearly we must also assume that their corresponding brothers, who showed little or no tremor (our own, none at any stage), were cases of the same disease. The importance of this conclusion lies in the fact that there is still some doubt as to whether tremor is not a constant symptom of lenticular disease whenever the motor cortex is functioning fairly normally. In our case there was never any evidence of severe cortical disease, and even post mortem, after a blazing tetanoid attack lasting nearly twenty-four hours, the degenerative signs in the cortex were comparatively light in degree. We therefore believe that in cases of lenticular disease tremor may be absent and its place may be taken by athetosis.

It will be noticed that Gowers refers to the movement in his case as choreiform; we have described ours as athetotic. The contrast in

Gowers' cases, together with such pictures as are available, drives us to the conclusion that we are both describing the same phenomenon in different words. We prefer the term athetoid because as a rule the complicated movement was of a slow writhing type, and not of the quick, jerky character seen in Sydenham's chorea.

The tremor described by Wilson as characteristic of his cases was essentially distal, and in our Case 2 the same observation was made. But in many other cases now published, notably those of Hall [17] and Strümpell [38, 39], it was proximal in type and tended to affect the neck and shoulder groups rather than the fingers. In some cases the tremor has been of the " intention " type, that is to say, the excursions were lateral and tended to become wider as the limb neared the completion of the intended action. In others it has been a rhythmic tremor present during rest, and capable of being controlled for at least a few moments by voluntary effort; in such cases the result of volitional activity has usually been to bring out a well-marked intention tremor of wide excursion.

Despite the varieties of tremor seen, no proved case of progressive lenticular degeneration has yet shown a tremor of the type usually seen in paralysis agitans, where tremors at (voluntary) rest and cessation of tremor during action is the rule.

It thus appears that the tremor which occurs in progressive lenticular degeneration may occur at rest, may occur only with voluntary movement and be of the "intention" or "action" type, or may be completely absent. The explanation is extremely difficult and much more investigation is necessary before a complete understanding of the reasons is possible. In the main it appears that the tremor only occurs when some voluntary effort is made either to move a limb or to maintain it in a specified position, as opposed to tremor which, in paralysis agitans, exists at voluntary rest. It may be that the cortex has such difficulty in overcoming the rigid resistance of the hypertonic muscles that the resultant action is only intermittent and thus gives rise to a rhythmic tremor. On the other hand, when the cortex is not acting it is clear that no tremor occurs such as is characteristic of the Parkinson syndrome.

The work of Ramsay Hunt [21] suggests that the latter condition is due to damage of the globus pallidus, which in our case was only slightly diseased. It may be that the absence of damage in this situation accounts for there having been no tremor, and that the severe damage of the putamen was the cause of the clinical symptoms of

athetosis and rigidity. This agrees with the observations of Anton [1] and Madame Vogt [41], who also came to the conclusion that the characteristic features of putamen disease were double athetosis, generalized rigidity and dysarthria.

Dysarthria and dysphagia.—These symptoms, and especially the former, were present in our cases as they have been in most of the proved cases of lenticular disease. The clumsiness of speech and difficulty of pronouncing labials have occurred early, and it may even already be present in our Case 4, though at present articulation is not so far abnormal as to be recognized as evidence of disease. Both defects appear to be due to a difficulty of overcoming resistance in the muscles involved in the necessary movements, and in this sense correspond exactly to the defect in motility in the limbs. The character of the speech, with its slow drawl and tremorless monotone, and with occasional explosive outbursts (in the earlier stages), contrasts with the equally monotonous and often slow speech of Parkinson's disease; for in the latter staccato elements are rare or absent, and the mouth remains only imperfectly opened. The widest contrast, however, is seen in the facial expression during speech, for in the cases we are describing efforts at speech call forth facial movements of an exaggerated type, whilst in paralysis agitans even the normal associated movements of facial expression are largely blotted out.

The facial expression in repose also contrasts forcibly with that seen in the Parkinson syndrome. In our type the general expression (fig. 7) is of pleased vacuity, the lower part of the face showing the greater departure from the normal; but in paralysis agitans all expression is largely lost, and only a suggestion of mournful expectancy remains. So constant are these contrasts that we have no difficulty in agreeing with Wilson that they cannot be dependent on identical lesions.

Hypertonus.—The two of our cases in which nervous symptoms developed to a serious stage both manifested a high degree of hypertonus, such as has been characteristic of all the cases described. In the earlier stages the resistance to passive movement was hardly above normal; in the later stages it became considerable, and in the premoribund stage in Case 1 it became intense. One observation made in our cases is worthy of attention, namely, that at one stage, when hypertonus was well developed and resistance to passive movement was considerable, this resistance tended to become less and less as the passive movements were rhythmically repeated, but recurred after a few minutes of rest. This observation agrees with that of Hall [17], who found the same feature in two of his cases.

The fact that one of our cases showed an extensor plantar reflex on the more severely affected side corresponds with the pathological finding of neuronal degeneration in the cortex; clinically it was accepted by us as indicating that the lenticular lesion was not a pure one. At the same time it needs emphasizing that the reflex was tested in the most delicate position, and that, with the knee bent, plantar excitation always gave rise to a flexor response; there existed, in fact, that delicate balance between flexor and extensor responses which one of us has described as "pyramidal equilibrium" [2]. The other reflexes, more particularly the abdominal, were consistently of normal character, until rigidity reached such a high grade as to make the observation of reflex movement valueless. The inference drawn was that in our cases such pyramidal disease as was present was of slight degree, and insufficient to affect materially the clinical picture.

An interesting early feature of Case 1 was the myotonic grip; this was so similar to that which is usually seen in Thomsen's disease that some doubt as to the diagnosis existed in the mind of an observer who was equally familiar with progressive lenticular degeneration. This proved to be a transient symptom, not present at a re-examination three months later, and not observed in other members of the family.

Other nervous symptoms.—The loss of emotional control so dominant in many cases of Wilson's disease was present in our cases only to a slight degree. On account of the difficulty of communicating with them and of their lack of education owing to prolonged absence from school, it was not possible to determine how far this emotional expression was a true index of feeling. The mental state of the patients, as far as could be ascertained, was backward but otherwise normal, neither undue depression nor abnormal exaltation occurring.

Emaciation in both Cases 1 and 2 was severe; it was not possible to determine how far it was the result of dysphagia or of cirrhosis of the liver.

Contracture developed, as expected, at a moderately advanced stage and resembled that described by previous authors. No fit or convulsion of an epileptic character has occurred in any of our cases.

Attention is drawn to the extraordinary symptoms present in our Case 1 during the period immediately preceding death. The clinical observer (S. B.) has had a large experience in observing cases of tetanus, and was struck by the almost exact similarity of the symptoms in this case to those occurring in the later stage of that disease. Had the child not been observed beforehand we are certain that the disease

would have been wrongly diagnosed as true tetanus, for the rigidity, the spasms produced by any apparent stimulus, the expression of anxiety, the sweating and pyrexia, combined to give a perfect picture of a patient in the throes of tetanus. It is unfortunate that no photograph is available of his condition at this period, but a full note was taken and is included in the clinical account.

Comparing the case with that of torsion spasm described by Blandy [3], it is interesting to note that, despite a general resemblance in that both suffered from severe persistent hypertonus accompanied by intense spasms, in our case the attitude was forward flexion of the head on the trunk, whereas in Blandy's case the head was drawn backward; in our case the legs were greatly affected by the spasm, and in hers hardly at all; the arms adopted the same position in both cases (extension and pronation).

We take this to mean merely a difference in the anatomical position of the damage, that in our case the lenticular control (release) of the extensors of the neck and back was less affected than the flexor control, and vice versa in Blandy's case; in each case both flexor and extensor action was damaged, but on balance the severer damage was present in different portions of the nucleus in the two cases.

The symptoms which occurred in Case 1 suggest an interesting speculation as to whether the cause of death in tetanus is not also a physiological obliteration of the lenticular nuclei and adjacent structures. The generally accepted theory that tetanus results from an irritation in the lower spinal reflexes is surely untenable in the face of these cases. The widespread nature of the spasms and the grouping of the muscles involved strongly suggest a damage at a much higher level, and that death occurs in this disease because the extrapyramidal control normally exercised through the basal ganglia and adjacent nuclei has been cut off by a paralysis of their activity.

The Liver.

All those who have described cases of hepato-lenticular degeneration have been struck with the severity of the cirrhosis of the liver contrasted with the paucity of clinical symptoms to which the liver disease had given rise. In fact, in the majority of cases no conclusive evidence that any disease of the liver existed had been obtained until a post-mortem examination was made. Thus in all Wilson's [45] cases liver symptoms were either absent, or slight and transitory. Gowers' cases [13, 14] of "tetanoid chorea" and Ormerod's case [28]

were without any history pointing to liver damage. Hadfield's case [16] suffered from no liver symptoms; Hall's cases in no instance gave unmistakable clinical signs of liver disease. On the other hand, Jendralski's [23] family of four cases (out of eight children) corresponded very closely in type and history to those recorded here; in fact one of the cases, after developing a Kayser-Fleischer ring, died of ascites and cirrhosis of the liver before any nervous sign had developed. In Kraupa's case also [26] jaundice was present for two years.

Other symptoms suggestive of alimentary disturbance, but not definitely pointing to the liver, have very frequently been recorded without, we think, due weight being accorded to their presence. These are attacks of diarrhœa and vomiting, migrainous headaches, hæmatemesis, epistaxis, occasional glycosuria and urobilinuria, and an irregular type of pyrexia which we think is caused by the acutely progressing hepatic disease.

Of our four cases, Case 3 died before any demonstrable nervous sign arose, and with a severe degree of ascites and some albuminuria. The subsidiary symptoms had been "bilious attacks," i.e., intermittent attacks of vomiting associated with headache and nausea, feverishness with a definite rise of temperature, and some costal pain. It was after a severe acute attack in which these symptoms predominated that the ascites began to accumulate, and the latter, together with the toxic effect of the liver damage, was the cause of her death. Case 1 (F. B.) also developed obvious signs of liver disease before any nervous damage arose; when he was 5 years old, and five years before his death, he had an illness in which attacks of vomiting (including hæmatemesis), probably light jaundice, certainly ascites (which was tapped), and a large hard liver edge, were prominent signs and symptoms. From this he made a symptomatic recovery, but his mother was sure that he was never "properly well" afterwards, and his nervous symptoms began to develop at this stage. Our Case 2 has had many attacks of "biliousness," i.e., of headache, vomiting, nausea, and occasionally a light degree of jaundice has been noticed. But though we cannot doubt that fundamentally the disease is the same as in Cases 1 and 3, yet no ascites or hæmatemesis has occurred though the nervous signs are now advanced. Case 4 is interesting as being still in the pre-nervous stage, but with a diagnosable liver damage. His liver is palpable and hard, and his symptoms have been intermittent feverish attacks accompanied by vomiting, diarrhœa, headache, nausea and slight jaundice.

Reviewing the published cases in the light of these records we cannot

fail to be struck by the fact that many of them have suffered in the earlier stages from vomiting attacks and bilious attacks, not demonstrably different from those recorded here. Such symptoms in a minor degree are so common, apart from gross disease of the liver, particularly in children, that no special significance has been attached to them; but we are convinced that in these cases they indicate definite attacks of acute hepatitis.

In general, the symptoms attributed to cirrhosis of the liver may be classified as obstructive and toxic. Of the former, ascites is a late example, and it occurs only when the disease is advanced and as a rule only when the peritoneum has undergone such secondary fibrosis as to render it incapable of absorbing the increased exudate. This is a process which tends to occur at an earlier stage in adults than in children, and may account for the relative paucity of cases on record in which ascites has preceded the lenticular symptoms in Wilson's disease; the rule will be that once ascites develops in such cases death is likely to occur before nervous signs appear. The earlier symptoms of the obstructive group will be hæmatemesis, "bilious attacks" and morning vomiting, whilst nausea, anorexia, light jaundice and urobilinuria will provide evidence of toxic damage to the liver cells. At one time or another all these symptoms have occurred in our cases, but during our observations they have never (except near the end in Case 3) so dominated the clinical picture as to compel the observer's attention.

It will be noticed that in three of our cases efforts have been made to determine the liver efficiency. In Case 1 the Van den Bergh test gave a negative result; the lævulose test could not be applied as he invariably vomited the sugar, whilst the hæmoclasic crisis failed to give any definite indication of liver insufficiency.

In Case 2, during a remission in which the temperature had been subnormal for eight weeks, the lævulose test was undertaken successfully and gave a negative result. A repetition of the test three months later gave again a normal result. In December, 1924, a third series of tests included the Fouchet and Van den Bergh (direct and indirect) tests, which were negative; tests for urobilinogen and urobilin in the urine, again both negative; and the ammonia coefficient was normal. Roch's test and the hæmoclasic crisis again gave negative results. These tests were done when we knew that a positive result was to be expected, but none indicated that the liver efficiency was impaired.

In Case 3, the child who died before any nervous symptoms were definitely manifested, the lævulose test showed a gross impairment of

liver function; but this test was carried out at a time when the patient was suffering from a recurrent attack of hepatitis which probably damaged the function of such liver-cells as had survived destruction caused by previous attacks.

Case 4, the child now aged 8, who has not yet developed nervous symptoms, was tested during an interval between attacks of hepatitis and when the temperature had been normal for several days; no evidence of liver insufficiency could be obtained by the lævulose test or by Van den Bergh's reaction.

These tests for liver insufficiency were all carried out with care under the direction of an expert clinical pathologist. We interpret them as meaning that even when the liver of such cases is in an advanced state of disease and very hard from the presence of much cirrhosis, a normal liver efficiency result may be obtained, provided that the acute attacks have subsided and have left a relatively large number of healthy liver-cells intact. But if the test is performed during the period immediately following an acute febrile attack (presumably acute hepatitis), then the liver-cells which have remained anatomically intact after earlier attacks are subject to such physiological damage that the liver as a whole fails to satisfy the metabolic demands of the individual.

No one reading the account of the repeated febrile attacks, with their associated signs and symptoms of enlarged liver, occasional icterus, vomiting and small hæmorrhages, can fail to be struck by their close similarity to those which occur in acute yellow atrophy of the liver. In Case 3 the final stages corresponded very closely, except that less jaundice was present and no petechial hæmorrhages occurred. The probable explanation is that previous disease had so damaged the liver that the acute hepatitis killed her before the graver symptoms of acute yellow atrophy appeared.

The histological findings in the liver of Case 3 also suggest that we are not dealing with a simple cirrhosis, the picture being one of a healing acute hepatitis or of the stage of repair in a subacute yellow atrophy.

Thus we conclude that in the cases we are recording here the liver disease is not a cirrhosis of a chronic, slowly progressive character, but that it is the result of a series of attacks of acute hepatitis, spaced over varying periods of weeks and months. Each attack tends on subsidence to leave behind some damage in the form of cirrhosis and destroyed liver-cells, and thus the liver becomes progressively more and more damaged. But there is a general tendency for the attacks of hepatitis

to become, after a certain stage, less and less severe (as in Case 2), and to occur at longer intervals; it is at this period that in our cases the nervous symptoms have appeared. Occasionally, however, the severity and frequency of the hepatitis is sufficient of itself to cause death before any nervous symptoms have time to appear in unmistakable form.

If it is true that the nervous damage is caused by a toxin which gains access to the brain by reason of the liver disease (whether developed in the liver or elsewhere), it must be clear that in cases such as we are describing the toxin has a selective action on the corpus striatum. It is a general physiological principle that if such a toxin acts in small doses over long periods before producing its end-results, such selective action will be relatively pure and much less contaminated by damage to structures of similar but not identical anatomical form and physiological function; on the other hand, a massive dose of toxin will rapidly destroy the function of the organ selected as its victim, but at the same time will overflow not merely to anatomically adjacent, but to physiologically similar structures. The variations noted both in the pathological findings and in the clinical symptoms in hepato-lenticular degeneration are probably to be explained on this basis. For example, in the case recorded by Howard and Royce [20], in which the whole disease process only lasted for five weeks, nephritis developed with severe symptoms of intense and widespread nervous damage, including spasms, contractures, tremors, &c., such as suggested a diagnosis of tetanus; histologically, not only were the lenticular nuclei damaged, but softenings were found in the thalamus, the red nucleus and the internal capsule. On the other hand, in Hall's [17] first case, where the disease lasted for seven years, the symptoms conformed much more closely to the Wilson type, and the disease, though not confined to the putamen, where the damage was intense, affected other parts of the nervous system but slightly. The deduction that pure lenticular lesions are to be expected in all long-standing cases cannot be made without reservation. It is clear from a consideration of our cases that the toxin is not being poured into the tissues constantly, but intermittently, the poisoning process presumably coinciding with the febrile attacks. It may then happen that a patient who has had several attacks which have left their mark upon the liver and brain in the form of cirrhosis and degeneration, may after a long latent period during which amelioration has occurred ("a remission"), receive in the next attack of hepatitis a massive dose of the toxin, which causes widespread damage; for

Nature's experiments in producing lenticular degeneration are not to be conceived as being conducted like a laboratory experiment where a carefully measured dose of the poison is presented to the tissues at specified intervals.

Thus we conclude that in hepato-lenticular degeneration the liver disease is always antecedent to the nervous damage, and that it consists in a series of acute attacks of inflammation (hepatitis) occurring at irregular intervals; that the toxin causing the nervous damage is entering the circulation and causing fresh nervous destruction during the acute attacks only and not during the "remissions," despite the fact that the cirrhosis of the liver may now have become a permanent factor.

An attempt was made in Case 4 to determine whether achlorhydria was present, and though a full test was impossible, it was proved that hydrochloric acid was present in the stomach. The close similarity of the cases may be taken to indicate that achlorhydria was absent also in the brothers and the sister of this case. Thus no analogy exists between this disease and that form of subacute combined sclerosis in which, as has been pointed out by A. F. Hurst [22], absence of hydrochloric acid is probably a factor in causing the disease.

The only toxic agent known to produce both liver and nervous disease is manganese. In chronic poisoning by this metal, cirrhosis of the liver and nervous symptoms resembling those of lenticular degeneration have been described by various authors, notably by Edsall and Drinker [7].

The experimental work of Marshall Findlay [9] is of great interest, despite the fact that no sign of lenticular disease was observed. He found that a single massive dose of manganous chloride (10 to 60 mg.) was extremely toxic to rabbits, and caused death in from twenty-two to forty-eight hours; the animal, after injection, gradually became quiet and listless, refused food, and passed into a semi-comatose state. At post-mortem examination the liver was large, friable, of a pale yellow colour, often with reddish mottlings; the spleen also was enlarged and as a rule of a deep red colour. On section the liver showed parenchymatous degeneration, amounting in some areas to definite necrosis, and acute glomerular nephritis was usually present. On the other hand, when rabbits were injected with smaller doses of manganous chloride repeatedly (3 to 5 mg. every second day), many of the animals survived for several weeks. The symptoms during this period were lassitude and anorexia (especially for a few hours after each injection), a

progressive loss of weight and an icteric tint in the tissues without any ascites. In these animals a post-mortem examination showed a new formation of connective tissues in the liver, and proliferation of the epithelium lining the bile-ducts. Wells [42] also has found that the repeated injection in rabbits of any foreign protein material, such as Witte's peptone, may be followed by cirrhosis of the liver.

More recently, Mella [27] has succeeded in producing rigidity and athetoid movements in monkeys by intra-peritoneal injections of manganous chloride. Histologically, he found neuronal degeneration and neuroglial overgrowth, particularly in the lenticular nucleus.

Edsall, Wilbur and Drinker [8] record cases of poisoning due to the inhalation of manganese dioxide under industrial conditions. The condition produced closely resembled paralysis agitans, in that the tremors, rigidity, cramps, mask-like facies and the propulsion and retropulsion were similar to those characteristic of the Parkinsonian syndrome. Attacks of uncontrollable laughter were, however, prominent in these cases.

These observations have a close analogy to our cases, both clinically and pathologically, but the clinical signs of manganese poisoning, although clearly of the extra-pyramidal type, are rather those of paraylsis agitans than of Wilson's disease; the toxin in manganese poisoning appears to select for its harmful activity portions of the nervous system other than those affected in Wilson's disease.

We have been unable to trace any means whereby our cases may have been subject to manganese poisoning. The facts that the large family of eight children have been living in one house, that four only of them have proved to be susceptible to the toxin, and that in no instance have two of the cases ever developed their acute hepatitic attacks concurrently, are almost sufficient to exclude the possibility of metallic poisoning from utensils used in cooking. The absence too of any vocation in which toxic substances may have been inhaled or introduced through the skin, throws us back upon the presumption that we are here dealing with toxins elaborated in the alimentary canal.

Interpreted broadly, the cases described here may be said to have suffered from repeated but usually mild attacks of "acute yellow atrophy" of the liver, each attack on subsidence leaving a permanent mark on the liver in the form of cirrhosis. From such attacks the liver was, up to a certain stage, capable of full symptomatic recovery; but once the liver damage had reached a certain grade the deficiency in its metabolic capacity appears to have permitted certain toxins or

poisonous food products absorbed from the alimentary canal to circulate in the tissues generally, and so to give rise to secondary damage in the central nervous system.

At this stage of our knowledge we can only speculate as to the place of origin of the primary focus of the disease. It is our hypothesis that in these cases there flourished amongst the flora of the alimentary tract some organisms which burst into activity at intermittent periods, in the same way as we believe does the *Bacillus typhosus* in a typhoid "carrier"; that its toxins pass through the portal system to the liver, whose cells in attempting to destroy these deleterious substances and so prevent a poisoning of the whole system are themselves so damaged in the effort that an acute hepatitis occurs in which many liver-cells die and others are put out of action for the time being. The toxin causing lenticular destruction might thus be either the primary alimentary one which escapes through the damaged liver where filtration capacity is in abeyance, or arise from the dying liver-cells themselves. On the whole, we favour the former alternative, seeing that in alcoholic and other forms of cirrhosis no nervous disease comparable to Wilson's type has ever been described, although the histological appearance of the final stages of the livers in alcoholic cirrhosis is so similar to that seen as an end-result in Wilson's disease.

Pathology.

Pathologically, the first case is clearly to be regarded as one of progressive lenticular degeneration. In nearly half the cases on which an autopsy has been conducted there has been no visible cavitation or softening of the lenticular nucleus, though in many of these the nucleus has been shrunken and of darker colour than normal. The association, as in this case, of cirrhosis of the liver with shrinkage of the putamen, and the microscopical finding in the latter region of neuronal degeneration, neuroglial overgrowth and new formation of capillaries, are almost as typical of the disease as is the cavity formation described by Wilson in his original article.

It must be emphasized, however, that although the degeneration in the putamen was the outstanding abnormality in the nervous system of Case 1, other regions of the brain were by no means normal. Considerable degenerative changes had taken place in the nerve-cells of the cortex, the neurons of the caudate nucleus were severely damaged, while those in the globus pallidus, cerebellum and to a less extent in the optic thalamus showed alterations from the normal. In all these regions

neuroglial reaction was evident, although there was no gross increase in the numbers of these cells. It is true that these changes were not comparable in intensity with those in the putamen; on the other hand it is obvious that the noxious agent did not have a strictly selective action on any one anatomical group of ganglion cells, or any one limited area of the central nervous system.

On the other hand, Case 3 was clinically one of subacute hepatitis without nervous symptoms, and it is therefore not surprising that the changes in the brain were of a somewhat different order. It is more than probable that except for the family history the brain would not have been examined or, at most, would have been examined macroscopically and accepted as normal.

There was no shrinkage or discoloration of the lenticular nucleus but, microscopically, there was a very definite outfall of the large nerve-cells of the putamen and degeneration of all the remaining elements, both large and small. There was no doubt that the changes were considerably more advanced here than in other regions, but, as in the preceding case, the cortical neurons and those of the caudate nucleus were also affected. The cells of the globus pallidus were only very slightly damaged; those of the optic thalamus and cerebellum were normal. There was nowhere any gross increase in the number of neuroglial cells but those present were hypertrophied. In addition a peculiar type of neuroglial cell was seen, in which the nucleus was enlarged to twice or thrice the usual diameter and strikingly pale, all the chromatin being aggregated into one or two intensely staining granules. Reference will again be made to these cells at a later stage.

The appearances in this case could not be attributed to a terminal infective process but were of a longer duration, probably to be estimated in months. We believe that they represented the earliest stage of a progressive lenticular degeneration which was abruptly terminated by an unusually severe affection of the liver. We wish to stress the fact that signs of inflammation were completely lacking in the nervous tissue. In other words, the process appeared to be a toxic degeneration with disappearance of nerve-cells, accompanied by neuroglial reaction and the production of a peculiar type of neuroglial cell; these changes, though widespread, were far more advanced in the putamen than elsewhere.

In their recent paper, Greenfield, Poynton and Walshe [15] state that, as the result of the investigations of the past ten years, progressive lenticular degeneration can no longer be accurately spoken of as a

system disease of the corpus striatum. The truth of this statement is becoming increasingly evident, and while in Wilson's original cases the morbid processes were almost exclusively confined to the lenticular nucleus, many of the more recent observers have described degenerations in other parts of the brain.

Stoecker [36, 37] found cystic degeneration in the putamen and, associated with this, widespread neuroglial changes in the cortex and elsewhere. Pfeiffer [31] alludes to degeneration of the ganglion cells of the cortex and red nucleus. Pollock [33] records slight changes in the cortical nerve-cells with an overgrowth of glia. Hadfield [16] found remarkable areas of vascular proliferation in the cortex. Howard and Royce [20] describe changes in the thalamus and red nucleus. Pollak's case [32] showed, in addition to softening and cavitation in the lenticular nucleus, an exactly similar condition in the white matter of the cerebellum involving a large part of the dentate nucleus. Finally Hall [17] observed marked degeneration in the putamen accompanied by slighter changes in most other parts of the brain.

The question here arises of the relationship between progressive lenticular degeneration and pseudo-sclerosis. As described by Wilson [45] and by Hösslin and Alzheimer [19], respectively, the two conditions appear very different, the former being a sharply defined destructive degeneration localized to the putamen, while the latter consists in a widely spread neuroglial overgrowth without destructive tendency. It has already been shown that such a conception of Wilson's disease is not now tenable, and a comparison of all the cases of both conditions reported before 1921 led Hall to consider them as essentially identical, and to describe them together under the term "hepato-lenticular degeneration."

The cases reported since the publication of Hall's monograph serve only to confirm this view. In particular, a case of "pseudo-sclerosis" recently described by Bouman and Brouwer [4] showed changes which, both in their character and distribution, closely resembled those in the first case recorded in this paper, although in their case the cortex was relatively more severely affected. The diagnosis of pseudo-sclerosis was made from the clinical symptoms, and it seems certain that if during life the alternative diagnosis of progressive lenticular degeneration had been made, these writers would have seen no reason to change it after the histological examination of the brain.

It is impossible to avoid the thought that, in some instances, the designation of a case as one of progressive lenticular degeneration has

caused attention to be directed too exclusively to the lenticular nucleus and that, in consequence, finer changes in other parts have been ignored. In a similar way the diagnosis of pseudo-sclerosis has led to emphasis being laid on the extra-lenticular changes. Thus the two conditions have been artificially separated. The classification of these cases under the term "hepato-lenticular degeneration" would remove the tendency to expect and over-emphasize certain alterations, and the changes in various regions would then be accepted at their true valuation.

A critical examination of the supposed points of distinction between pseudosclerosis and progressive lenticular degeneration shows how indefinite is the border-line which separates them. As an example may be cited the greenish pigmentation of the cornea first mentioned by Fleischer in pseudosclerosis, and for a considerable time considered pathognomonic of that disease but now recognized as occurring in both diseases.

Histologically, the chief point relied on in the differential diagnosis of the two conditions and emphasized by Alzheimer, Wilson and others, is the presence in pseudosclerosis of certain peculiar neuroglial cells usually known as "Alzheimer cells." They exist in large numbers in many regions of the brain and are giant cells with no tendency to fibre formation. The nucleus has a diameter of about six times that of an ordinary neuroglial nucleus, and is extraordinarily poor in chromatin but possesses often a single, intensely coloured nucleolus. The nucleus is often indented or lobed and the nuclear membrane much wrinkled. In Nissl preparations the cytoplasm is not always seen.

Spielmeyer [35] has shown, however, that these cells are also found in cases of progressive lenticular degeneration, in which they are not localized to the lenticular nucleus but occur in many parts of the nervous system. He comments on their very close resemblance at times to nerve-cells. They may sometimes contain intensely blue-coloured granules or masses of greenish pigment. The former stain exactly like the nuclear chromatin and are often very plentiful in those cells possessing a nucleus strikingly poor in chromatin, suggesting that there is a relation between the presence of these granules and the disappearance of chromatin from the nucleus.

In discussing the Alzheimer cells, Campbell and Morse [5] state that "Even the polymorphous glia, which has been considered (wrongly) almost pathognomonic of pseudosclerosis is found in various toxic and infective processes although not in such abundance as in pseudosclerosis."

In the first case here recorded a few cells of this type were found in the cortex and basal ganglia, but were far from numerous. In the third case a peculiar type of neuroglial cell was present which possessed some of the characters of the Alzheimer cells. The nuclei were round or oval in shape and of comparatively small size, attaining at most a diameter of three times the normal. The nuclear membrane was never wrinkled and a nucleolus was not present. The nucleus was, however, extraordinarily poor in chromatin and appeared as an empty vesicle except for one or perhaps two small intensely staining granules. These cells were quite unlike any of the ordinary types of reactive neuroglia, and probably represented a stage in the formation of the Alzheimer cells or a variant of that type of cell. Up to the present time we have never seen this type of cell or the Alzheimer cell in any other condition, and we cannot therefore confirm the statement of Campbell and Morse that the latter are found in other toxic and infective conditions.

The liver in the third case presented an unusual and suggestive picture, namely, that of a healing subacute yellow atrophy. Plasma cells were present in the fibrous tissue-strands, suggesting an inflammatory basis for the condition. In many of the cases described previously a very marked vascular proliferation has been a prominent feature, and to this and to the considerable regenerative powers of the liver in young subjects Hall ascribes the absence of symptoms of liver disease. Neither process was very prominent in this case and it would seem that here the noxa had been more than usually intense.

The association of well-marked disease of the liver with very early stages of degeneration in the brain points to the former as the primary condition.

Papadato [30] has suggested that progressive lenticular degeneration is nothing more than the result of an encephalitis, probably encephalitis lethargica. He accounts for the absence of inflammatory phenomena in the brain by the long duration of many of the cases, which allows sufficient time for the inflammation to subside so that after death only its results are evident to the histologist. Moreover he believes that the encephalitic process is the primary one and that the cirrhosis of the liver is the result of a secondary affection of that organ.

Westphal and Sioli [44] describe a case in which the symptoms of progressive lenticular degeneration followed an attack of what was probably encephalitis lethargica and which showed the histological features of both diseases.

In the case of pseudosclerosis described by Campbell and Morse [5], the development of the disease was accompanied by recurrent attacks of facial erysipelas. Histologically there were, in addition to the usual changes found in pseudosclerosis, appearances which they think may well be regarded as inflammatory in nature, for example, slight lymphocytic infiltration around isolated vessels in the cortex, thalamus, hypothalamus and midbrain, a moderate general thickening of the arterioles, moderate proliferation of the capillaries in the cortex, corpus striatum and midbrain, swelling of the capillary endothelium in the cortex and midbrain, and œdema, thickening and cellular infiltration of the pia.

On the other hand, neither Hall, Stoecker nor Spielmeyer have found any evidence of an inflammatory process in progressive lenticular degeneration or pseudosclerosis. In neither of our cases were there any appearances of inflammation, although Case 3 showed a very early stage of the process at which inflammatory signs might be expected if they did occur. In any chronic nervous disease there is a tendency to the involvement of the brain in a terminal or coincident infective process and the resulting picture cannot be accepted as other than an accidental occurrence. That progressive lenticular degeneration is a late result of encephalitis lethargica is negatived by the fact that the pathology of the two diseases is entirely distinct. Although certain changes in the liver have been described in the latter condition, they are comparatively slight, and no case has been described in which there has been found a picture even remotely resembling that in Wilson's disease.

Finally we must touch upon the relation between neuroglial reaction and neuronal degeneration. Having regard to the appearances produced in a variety of nervous diseases, it can no longer be supposed that the two go hand in hand, or that the former is dependent upon or necessarily originated by the latter. There are numerous types of neuroglial reaction, some of which seem undoubtedly to be caused by the degeneration of the nervous elements and others which can only be ascribed to a direct action of a noxa on the neuroglia independent of, though perhaps accompanied by, nerve-cell destruction. In the diseases under discussion the neuroglial response is often widespread when nerve-cell degeneration is comparatively sharply localized to the lenticular nucleus, and it is often seen to be well marked in areas in which the nerve-cells are comparatively well preserved.

It appears, then, that in hepato-lenticular degeneration an inflammatory condition arises in the liver which, by virtue of its chronicity in

the majority of cases, coupled with the considerable regenerative power of the affected organ in a young subject, tends to be latent or give rise to only slight indications of its presence. A toxin or toxins, which have a specific effect on the nervous system, are produced in, or allowed to pass through, the damaged liver. Acting on the neuroglia, a peculiar and diffuse reaction is set up which is characterized by the production of Alzheimer cells, and when this process is predominant the case is one of pseudosclerosis. The same or more probably another toxin acting on the neurons and affecting especially those of the neopallium induces their degeneration and a "progressive lenticular degeneration" is the result. In the majority of instances both of these processes occur, but in different degrees, so that a whole series of links is found between the two extremes of pseudoclerosis and progressive lenticular degeneration.

Diagnosis.

The nervous signs occurring in pseudo-sclerosis appear to be much less distinctive than in Wilson's disease. The earlier cases described under the former heading by Westphal [43] and Strümpell [38, 39], which were not stated to be associated with liver disease, showed much diffuse degeneration in the cortex as well as the basal ganglia; the symptoms were much less clearly defined, and in fact are hardly comparable to those described by Wilson in his original monograph. But it seems clear to us that most of the later cases—as, for instance, Fleischer's [12] (published under the title of a "Hitherto unknown Disease allied to Pseudo-sclerosis"), Rausch and Schilder's [34], and Oppenheim's [29]—are simply varieties of the Wilson type of lenticular degeneration. Recalling the fact that the anatomical distribution of the lesion is not confined to the putamen, that this nucleus is often incompletely destroyed, and that all cases carefully investigated have shown some damage in other parts of the corpus striatum or cortex, it is natural to expect that the symptoms will not in all cases exactly correspond. At least two other factors must be considered as affecting the symptomatology; one is the age of the patient, and another the rapidity and intensity of the disease-process. In practically all the younger patients, and especially those under the age of 10 years, spasm (tonic and clonic), athetoid movements and "choreiform" movements tend to predominate to the exclusion of tremor; in older patients (above the age of puberty) tremor has been the most obvious involuntary movement. Again, in the acute cases in which the whole course of the disease is run within a few weeks or months, spasm and writhing movements tend to be prominent features and tremor may be completely

absent (Economo [6], Thomalla [40]). Finally, the stage at which the clinical description is obtained must determine to some extent whether tremor is described or not. In the earlier stages, where the damage may be closely confined to the putamen and the pallidum retains its physiological function, it would appear that tremor is usually absent; when the degeneration has progressed and has begun to involve the globus pallidus, there is a general tendency for tremor to cease to be dominant in the clinical picture.

Ultimately, the classification of the types of lenticular disease must depend not so much on the clinical symptoms and the anatomical localization of the lesion, as upon the origin and character of the disease process. In so far as cases conform to the general type, that is if they show a damage of the liver of the special and unusual type which we have described, and which we believe to be a cirrhosis resulting from repeated attacks of acute hepatitis, if they later develop disease mainly located in the lenticular nuclei, then we are of opinion that they should be classed together as one definite type of disease. The occurrence of that rare phenomenon, the Kayser-Fleischer line (corneal pigmentation), is proof of the special type of liver cirrhosis which is capable of producing such nervous disease.

Thus we would classify most of the cases described under the title "pseudosclerosis" as cases of hepato-lenticular degeneration, and would hope that the former term will be allowed to lapse, an opinion which we share with Hall [17], Greenfield, Poynton and Walshe [15], and many others who have written recently on this subject.

Thomalla's [40] torsion spasm (dystonia musculorum deformans) seems to us to belong to this group. The characteristic liver, the occasional presence of the corneal ring, the location of lesions in the lenticular nuclei and the general clinical picture of rigidity, mobile spasm (not widely different in type from the athetoid movements we have described), all suggest that we are dealing with the same essential disease with a localization of damage differing only in position from that seen in Wilson's disease.

On the other hand, not all cases of lenticular disease are of this type. Those which are congenital or due to vascular lesions, and the syphilitic forms, despite the damage which occurs in them to the lenticular nuclei, must have an origin which is totally different in type. Even manganese poisoning cannot be identical, though conforming to type in that both the liver and extrapyramidal nervous tissues show damage, for in this case the toxin has clearly a different selective

action, has never (as far as observation has gone) given rise to a corneal pigmentation or produced nervous signs significant of progressive lenticular degeneration.

Nomenclature.

Only the gravest of reasons would be adequate to warrant any alteration of the title of the disease which was so ably evolved from a chaotic conglomeration of cases by Wilson in 1912. Progressive lenticular degeneration is a good name in that it indicates both the anatomical lesion responsible for the outstanding symptoms, and the progressive character of its incidence. It fails only in that it does not indicate in any way that the disease is associated with cirrhosis of the liver, and as this event is almost unique in neurological experience, some suggestion of its presence would be better included in the title. Further, as we have tried to prove in this article, the liver disease is primary both in time and in importance, in that progressive lenticular degeneration never occurs apart from such a physical foundation. Again, other types of what we regard as the same disease, namely, pseudosclerosis and torsion spasm, together with the tetanoid chorea which was accepted by Wilson as a variation of his disease, appear to have the same fundamental pathology. In cases of these diseases, manifest or latent, and in no others, has the Kayser-Fleischer zone of corneal pigmentation been observed, and all authentic cases are associated with liver disease.

For these reasons we have come to the conclusion that it would be better to adopt Hall's [17] terminology, and refer to the condition as hepato-lenticular degeneration. As in so many cases where names employed for diseases are descriptive, this title fails to indicate the peculiar type of the disease in the liver (namely, that it is the end-result of a series of attacks of subacute or acute hepatitis), but it indicates clearly enough that the lenticular disease is a sequel to liver damage and is of the type of progressive degeneration.

Conclusions.

(1) Wilson's "progressive lenticular degeneration," Gowers' "tetanoid chorea," certain cases of "pseudosclerosis" and Thomalla's "torsion spasm"—should be grouped together as forms of "hepato-lenticular degeneration."

(2) The nervous symptoms of this disease never occur until the liver has been grossly damaged. The hepatic cirrhosis seen post mortem is an end-result of a series of attacks of acute hepatitis.

(3) The toxin causing the hepatitis is not manganese. It probably has a bacterial origin in the alimentary canal.

(4) The variation in clinical nervous symptoms depends partly upon which regions of the lenticular nuclei are mainly damaged, and partly upon the degree to which damage is done to other nervous structures.

POSTSCRIPT.—Whilst the foregoing article was being set up. Case 2 (Phœbe B.) died during September, 1925. The organs, including both corneæ, are available for histological examination, and it is hoped to publish an account of them in a later number of this Journal.

REFERENCES.

[1] ANTON. *Journ. of Psych.*, 1895, **14,** 141.
[2] BARNES, S. *Rev. Neurol. and Psychiatr.*, 1904, **2,** 345.
[3] BLANDY, M. *Journ. Neurol. and Psychopath.*, 1920, **2,** 14 B.
[4] BOUMAN and BROUWER. *Psychiatr. en Neurol. blad.*, 1922.
[5] CAMPBELL and MORSE. *Journ. Neurol. and Psychopath.*, 1924, **5,** 28.
[6] ECONOMO, C. *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1919, **33,** 173
[7] EDSALL and DRINKER. "Contributions to Research," 1919, **1,** 447.
[8] EDSALL, WILBUR and DRINKER. *Journ. of Indust. Hygiene*, 1919, **1,** 183.
[9] FINDLAY, G. M. *Brit. Journ. Exper. Path.*, 1924, **5,** 92.
[10] FLEISCHER. *Klin. Monatsbl. f. Augenheilk.*, 1903, **41,** 489.
[11] *Idem. Münch. med. Woch.*, 1909, **56.1,** 1120.
[12] *Idem. Deutsch. Zeitschr. f. Nervenheilk.*, 1912, **44,** 179.
[13] GOWERS. "Diseases of the Nervous System," 1893, **2.**
[14] *Idem. Rev. Neurol. and Psychiatr.*, 1906, **4,** 249.
[15] GREENFIELD, POYNTON and WALSHE. *Quart. Journ. Med.*, 1924, **17,** 385.
[16] HADFIELD. *Brain*, 1923, **46,** 147.
[17] HALL. "La dégénérescence hépato-lenticulaire," Paris, 1921.
[18] HOMEN. *Arch. f. Psych.*, 1892, **24,** 191.
[19] HÖSSLIN and ALZHEIMER. *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1911-12, **8,** 183.
[20] HOWARD and ROYCE. *Arch. Int. Med.*, 1919, **24,** 497.
[21] HUNT, J. RAMSAY. *Brain*, 1917, **40,** 58.
[22] HURST, A. F. *Brain*. 1925, **48,** 218.
[23] JENDRALSKI. *Klin. Manatsbl. f. Augenheilk.*, 1922, **69,** 750.
[24] KAYSER. *Klin. Monatsbl. f. Augenheilk.*, 1902, **40,** 22.
[25] KOBY. "Slit-lamp Microscopy of the Living Eye," (Trans. Goulden and Harris), London, 1925.
[26] KRAUPA. *Klin. Monatsbl. f. Augenh.*, **69,** 526.
[27] MELLA. *Arch. of Neurol. and Psych.*, 1924, **2,** 405.
[28] ORMEROD. *St. Bart.'s Hosp. Reports*, 1890, **26,** 57.
[29] OPPENHEIM. *Neurolog. Centrabl.*, 1914, **33,** 1202.
[30] PAPADATO, *L'Encéphale*, 1925, **20,** 14.
[31] PFEIFFER. *Journ. Nerv. and Ment. Dis.*, 1917, **45,** 289.
[32] POLLAK. *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1922, **77,** 37.
[33] POLLOCK. *Journ. Nerv. and Ment. Dis.*, 1917, **46,** 401.
[34] RAUSCH and SCHILDER. *Zeitschr. f. Nervenheilk.*, 1914, **2,** 414.
[35] SPIELMEYER. *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1920, **57,** 312.
[36] STOECKER. *Ibid.*, 1913, **15,** 251.
[37] *Idem. Ibid.*, 1914, **25,** 217.
[38] STRÜMPELL. *Deutsch. Zeitschr. f. Nervenheilk.*, 1898, **12,** 115.
[39] *Idem. Ibid.*, 1899, **14,** 348.
[40] THOMALLA. *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1918, **41,** 311.
[41] VOGT, C. *Journ. f. Psych. u. Neurol.*, 1912, **18,** 479.
[42] WELLS. "Chemical Pathology," Philadelphia, 2nd edition, 576.
[43] WESTPHAL, C. *Arch. f. Psychiatr. u. Nervenheilk.*, 1883, **14,** 87.
[44] WESTPHAL and SIOLI. *Arch. f. Psychiatr.*, 1922, **46,** 747.
[45] WILSON, S. A. K. *Brain*, 1911-12, **34,** 295.
[46] *Idem.* "Questions neurologiques d'actualité," Paris, 1921, p. 1.
[47] *Idem.* "Oxford Loose Leaf Medicine," New York, 1921, **6.**

THE CENTRAL TRACTS OF THE NERVUS VESTIBULARIS.[1]

BY ISAAC H. JONES, M.D. (LOS ANGELES),
AND
WILLIAM G. SPILLER, M.D.
Professor of Neurology in the University of Pennsylvania, Philadelphia.

In the attempt to determine the central vestibular pathways, those who have undertaken experimental work on animals have encountered two main difficulties: the limitation of secondary degeneration owing to interruption at synapses, and the obvious difficulty in producing minute lesions in certain portions of the brain-stem without disturbing adjacent structures. In order to trace any particular pathway throughout these various segments it would be necessary to produce lesions such as to involve each neuronal segment in turn. These difficulties appear almost insuperable.

On the contrary, certain pathological processes occasionally result in small discrete lesions within the central nervous system which cannot be duplicated by operative work on animals. Such lesions may be produced by thrombosis, small foci of encephalitis and multiple sclerosis.

The case of epidemic encephalitis to be reported presented the following features: Examination revealed an absence of vestibular function, with no impairment of auditory function. A persistent spontaneous nystagmus existed of a type suggestive of a central vestibular lesion. Examinations and tests were made just before death, which occurred suddenly and was probably attributable to the brain-stem lesion. The autopsy revealed nothing abnormal, thus indicating that there were no pressure phenomena and that the lesion was microscopic.

A. C., aged 15, of American parentage, was born and lived all his life in California. His father died of pulmonary tuberculosis; his mother and two older brothers are living and well.

Previous medical history.—His birth was normal. In early childhood he had measles, mumps and whooping-cough. He was always full of energy and

[1] Read before the American Neurological Association, May 6, 1925.

active in school athletics; in fact he was a leader in the school sports, particularly in gymnastic work. He could walk on his hands almost as well as on his feet and excelled at baseball, basketball, football and in tumbling. He had a good record in his scholastic studies and was in his second year at a high school. He had an attack of "influenza" in 1918, and another similar attack in the winter of 1922.

Present illness.—In February, 1923, he had another attack of influenza. In May, 1923, he complained of fatigue and of being "short of wind." On exercising "his legs hurt and he would be covered with a cold sweat." On getting up from a sitting or lying position he was unable to move about without holding on to something to steady himself. He would grasp a table and put his hands over his eyes. At times he would have to lie down again. Before this he had been putting on weight and "felt better than he ever had in his life." The first symptoms noted were his inco-ordination and disturbance of equilibrium in walking and a gasping for breath. He finished his school year, although with considerable effort.

On July 14 he became acutely ill. He felt cold and a cold sweat was noted; this condition lasted all night. Early the next morning his mother noticed him lying in bed perfectly still and unconscious. She could not arouse him and thought he was dead. She stated that there was no motion of his body and she could not see him breathe. This condition of unconsciousness lasted for two hours. On recovering consciousness he "gasped for breath." His mother states that the physician told her that "his pulse was good." On recovering consciousness he was able to swallow and recognized his family; he then relapsed into unconsciousness for short intervals and had attacks in which his face jerked, his hands moved and his head was thrown back, but there was no frothing at the mouth, no biting of tongue and no involuntary urination. A convulsion would last two to three minutes and they were about five minutes apart. He remained unconscious for a short time following each convulsion. These convulsions continued for about two hours and then ceased. He was kept in bed for one week, at the end of which time he walked from the house to the automobile and went to the hospital. He was suffering no pain. The only physical findings were "rapid pulse, a slight murmur at the pulmonic area and a high blood pressure." He stayed in the hospital one week and left it apparently in good condition. He was kept in bed all the summer "on account of his heart." During the summer of 1923 he did not sweat during the day, but as soon as he dropped off to sleep he became wringing wet; even if covered with only a sheet water would pour off him. This sweating would continue until about 2 o'clock. This happened every night. On no occasion did he sweat after 2 o'clock in the morning; his mother was sleeping in the same room with him and she made observations from time to time every night. After 2 o'clock in the morning she would change his night clothes and there would be no further sweating.

He had no more attacks and felt apparently well until September 19, when he ate some grapes which caused him to strangle and to gasp for breath.

There was no coughing and no vomiting. He found it difficult to get his breath during that day. He was able to eat solid food but had difficulty in swallowing liquids. A few days later he went to sleep but in a few minutes he awoke frightened, "ran to the window for air, and gasped for breath." He felt as if someone were "holding on to his windpipe." He had a convulsion with muscular twitching which lasted a few minutes, but he was not unconscious. Several nights after going to sleep he had similar attacks. These, however, were not so severe and not of so long duration. Two months before his death he was very unsteady on his legs. He said they "felt like sticks and as if they did not belong to him." He had poor control over them and at times could not walk in a straight line.

On February 20, 1924, he was taken to Dr. C. E. Reynolds, who reported that he had had attacks of gasping for breath and dysphagia during December, 1923, and January and February, 1924. The optic discs were slightly blurred at the nasal edges. Taste and smell were normal: the heart sounds were feeble, the blood-pressure was 110—70, the pulse 92, temperature was 99·2° F.; the tongue was very furred. Slow, coarse nystagmus, mostly to the right, existed. The Romberg sign was negative. Intention tremor and ataxia were present in both arms, more marked on the left side. The patellar reflexes were active and equal. Babinski's sign was negative at first, but was positive on the right side on February 24. The pupils were equal and normal; they reacted well to light and on accommodation, but convergence was imperfect. During Dr. Reynolds's observation the patient had a tonic emprosthotonic fit. The diagnosis of encephalitis was made.

In March, 1924, through the courtesy of Dr. Reynolds, the patient was examined by Dr. Ingham, Dr. Lyster and Dr. Jones.

Neurological examination by Dr. S. D. Ingham.—Patient was tall for his age (15 years), was well developed and fairly well nourished. Speech was monotonous and not very well enunciated. He frequently smiled and laughed but without a natural appearance; there was a lack of mobility of expression. Attempts to cough were ineffectual; sneezing was not observed. Conjugate deviations of the eyes to the right and the left and downward were practically normal; upward movements were definitely impaired and attempts at convergence failed almost entirely. There appeared to be a definite defect in accommodation. The pupils were equal and reacted to light. Facial expression simulated the mask of paralysis agitans. He had no loss of voluntary movements of the muscles of mastication or of the face, tongue or palate, and no wasting or tremors. Voluntary motor functions were generally impaired, and he had lost the ability to exercise with the gymnasium apparatus. The tendon reflexes were present in all extremities and were slightly excessive but equal on both sides, without clonus. The plantar reflexes were flexor in type. He walked slowly with his body slightly forward. Romberg's sign was negative. The arms were held in a rigid position without swinging; passive motion showed some increase over the normal resistance in both upper and lower extremities; he had no tremors or forced movements of the face, hands or feet.

Co-ordination was fairly accurate in the finger-to-nose test, but the spontaneity of voluntary movements was impaired.

Mental condition: patient was bright and alert, and of more than average intelligence; he appeared to be in complete possession of all his mental faculties, gave accurate details of his history and the members of his family had noticed no loss of mentality. No emotional or psycho-neurotic symptoms had been observed.

Ocular examination by Dr. T. C. Lyster.—The boy had never worn glasses. About June, 1923, he began having periods of "blindness" lasting about half a minute, then vision became clear. The attacks of temporary blindness came on suddenly and the return to normal vision was slow. The vision of his right eye was 6/V.1-2 and of his left eye 6/V.1-3; near vision and accommodative power were poor. Examination of his eyes showed the following abnormalities: the movements were slightly limited in all directions, especially upward and convergence; on looking up his eyes soon began to sag downwards and at the same time showed an undulating form of movement up and down. The retinal vessels were somewhat dilated and more tortuous than normal, with poor reflexes; the disc margins were fairly well defined. The visual fields showed a moderate peripheral concentric contraction for white; both blind spots were almost normal in size. Under homatropin dilatation there was found an error of hypermetropic astigmatism with one degree of right hyperphoria; vision improved to 6/V.1 in each eye when corrected.

Ear, nose and throat examination by Dr. I. H. Jones.—The nose was normal, except that the left naris was partially obstructed by a septal deviation. The teeth were in fair condition. He had a peculiar formation of the upper jaw, like a horseshoe flattened in front. He had chronic purulent tonsillitis, the tonsils being large, deeply buried and containing many large crypts with an unusually large amount of "creamy" material, especially in the upper pole of the left tonsil. He had chronic pharyngitis and moderate cervical adenitis in the anterior chain on each side.

Ears.—Both drum-membranes were somewhat retracted and somewhat opaque, showing evidence of moderate chronic catarrhal change in both middle ears.

Examination with the audio-amplifier by Professor Vern O. Knudsen and Dr. Jones revealed normal auditory function in both ears. The patient said that his hearing was normal. There was no deafness in his family. He had never experienced any tinnitus. Tests with the amplified voice and whisper indicated that he heard distinctly with both ears. The audiometric findings are shown in the accompanying audio-amplifier charts. These indicate a slight impairment of conduction. For example, for low tones his hearing was 80 per cent., for the high tones it was approximately 100 per cent. The upper limit of audibility was 17,000 d.v. for the right and left ears. His hearing by bone conduction at 256 d.v. was 100 per cent. in both right and left ears. There was no evidence of diplacusis or tonal islands. The conclusions from the findings were that both cochleæ and their neural pathways were functioning perfectly.

MEASUREMENTS WITH AUDIO-AMPLIFIER.

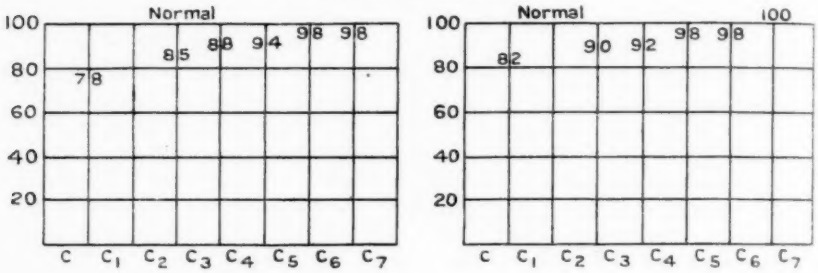
RIGHT EAR. LEFT EAR.

I.—*Amplifier.*

Voice, distinct Yes Voice, distinct Yes

Whisper, percentage hearing 97 % Whisper, percentage hearing 100 %

II.—*Percentage Hearing for Tones.*



III.—*Upper Limits of Audibility.*

17,000 d.v. Perfectly normal. 17,000 d.v. Perfectly normal.

IV.—*Bone Conduction.*

128 , 256 100 % , 512 . 128 , 256 100 % , 512 .

V.—*Special Findings.*

(Pitch and loudness of tinnitus, diplacusis, tonal islands, etc.)

No special findings.

Diagnosis: Slight conductive impairment in each ear, slightly more marked in right.

Comments: Otherwise normal auditory functions. Perfect function of both cochleæ.

Note: C – 64 d.v., C_1 – 128 d.v., C_2 – 256 d.v., C_3 – 512 d.v., C_4 – 1024 d.v., C_5 – 2048 d.v., C_6 – 4096 d.v., C_7 – 8192 d.v.

Vestibular report.—He had spontaneous nystagmus: on looking straight ahead there was a spontaneous nystagmus of an indefinite character; the eyes were constantly moving but the amplitude of the movements was small. The nystagmus was somewhat rhythmic in character, but one could not determine that the quick component was in any definite direction. The eyes wavered in different directions. The lower and upper eyelids also moved synchronously with the movement of the eyeballs. When the patient looked voluntarily in different directions, the most conspicuous movement occurred

when he looked up; then there was a vertical nystagmus, but the quick component was not definite and the nystagmus was not actually rhythmic; one could simply say that there were vertical movements of the eyes on looking up. The movements were slow. On looking to the right there was a mixed horizontal and rotary nystagmus to the right of fair amplitude. On looking to the left there was a mixed horizontal and rotary nystagmus to the left, the horizontal element predominating. On looking down he had no nystagmus. Spontaneous pointing: the right arm past-pointed 1 in. to the left. The left arm past-pointed 1 in. to the right.

Rotation tests.—After rotation to the right no horizontal nystagmus to the left developed, in fact there was no response that could be traced to the rotation and even immediately after it ceased there was no change in the already existing spontaneous nystagmus, and no change in the past-pointing, the right arm still past-pointing 1 in. to the left and the left 2 in. to the right. In other words the rotation failed to produce any change in the pointing. Rotation to the left similarly failed to produce nystagmus or past-pointing.

Rotation to the right with the head forward caused the patient to lean slightly to the right when he sat up, while rotation to the left with the head forward caused him to lean a little more to the left. All these rotation tests were conducted one after the other without producing pallor, sweating or nausea.

Caloric tests.—Irrigation of the right ear with the head thirty degrees forward (vertical canals) produced no response in nystagmus or past-pointing. On tilting the head backward (testing the right horizontal canal) there was also no nystagmus or past-pointing, and Romberg's test was negative when he stood up. Irrigation of the left ear with the head thirty degrees forward produced no alteration in the nystagmus or past-pointing. On tilting the head backward (testing the left horizontal canal) there was no nystagmus or past-pointing, nor any tendency to falling when he stood up with his feet together and his eyes closed,

All the rotation and caloric tests were conducted one after the other, and yet there occurred no pallor, sweating, or nausea.

In sharp contrast to the perfect auditory function in both ears there was absence of vestibular functions in both. The rotation and caloric tests failed to produce nystagmus, vertigo, past-pointing, falling, pallor, sweating, or nausea. There was, therefore, a complete vestibular block, the location of which appeared to be within the brain-stem shortly after the entrance of the eight nerves into it. Nothing in the examination indicated any lesion in the vestibular portion of either the internal ears or eighth nerves.

Patient died eleven days later, on March 17. Respiration became more and more rapid and shallow and irregular. He was taken to a hospital at eleven o'clock in the morning and died at two o'clock the next morning. Intellect was apparently keen. He recognized his school teacher on the night he died and tried to talk to him, but could not do so. His mother and others present stated that he apparently heard everything that was said to him. He

suddenly became comatose and deeply cyanosed. It was noted that in contrast to the respiratory difficulty the pulse was of comparatively good quality.

The autopsy was performed by Dr. Reynolds and Dr. Hammack. No lesion was observed in any portion of the brain or membranes, except undue hardness and whiteness of the medulla oblongata. The whole brain was removed and sent to Dr. William G. Spiller, whose report follows.

The brain-stem from the lower portion of the medulla oblongata to the end of the aqueduct of Sylvius was cut in microscopical serial sections, over 1,000 in number, and a very large proportion of these were stained, every third or fourth section at some levels, by various methods.

The important finding was a limited area of complete degeneration in the centre of the tegmentum, extending from the lower part of the medulla oblongata well into the lower part of the pons, with the raphé as its centre.

It may be concluded from this study that all or nearly all of the central tracts concerned with vestibular function pass through the area represented by this degeneration, and that few of the fibres of the cochlear system are represented in this region. The radicular fibres of the nervus vestibularis and the nervus cochlearis escaped entirely. The degeneration involved only the central tracts of the vestibular system.

Important degenerative changes in the form and number of nerve cells in the primary nuclei of the nervus vestibularis were found, and an attempt is made to correlate these nuclear lesions with the central area of degeneration. A part of the medulla oblongata from its lower portion was examined by the method of Marchi, but the formalin hardening produced so many artefacts that this method of study was abandoned, as it was believed that the results would be misleading.

The description of the findings in detail is as follows :—

At the level of the exit of the nervus vagus and the nervus hypoglossus there is a very small area of degeneration on each side of the raphé nearly symmetrically situated, implicating slightly each nervus hypoglossus. At the outer portion of each of these areas there is another very small area of degeneration, the one on the right side being the larger, and some of the fibres passing to the nucleus olivaris are involved. Each nervus vagus escapes entirely and the involvement of each nervus hypoglossus is very slight. The raphé is not implicated at this level by the areas of degeneration, nor are the longitudinal fibres on each side of the raphé. The number of fibres contained in the striæ medullares are diminished.

At a little higher level the extreme left area of slight degeneration has disappeared, but the corresponding one on the right side remains.

At the upper level of the exit of the nervus glossopharyngeus and below any portion of the nervus octavus, or possibly at its lowest part, the areas of degeneration are much the same (section 19). The fibres decussating at the posterior part of the raphé and those near the nucleus olivaris are nearly normally numerous, but those in the middle portion of the raphé are very scanty.

At the level of the entrance of the nervus cochlearis (section 29), the area of degeneration on each side has approached close to the raphé, and the more ventral arciform fibres are scarcely involved, only a little so on one side, but the middle arciform fibres are very scanty. The most caudal of the fibres of the corpus trapezoides may be a little involved on one side.

FIG. 1.—Section 9. Separate areas of degeneration on each side of the raphé.

At a little higher level (section 33), the two areas of degeneration have united into one central area and the raphé at this point is degenerated. The degenerated area extends as a transverse band across the central part of the medulla oblongata, and is well posterior to each nucleus olivaris, so that the striæ of Held and the corpus trapezoides are not involved. The nucleus ambiguus shows evidence of encephalitis.

At a little higher level the nervus vestibularis (section 40) has appeared. The central area of degeneration maintains the same relative position throughout the medulla oblongata. At the level where the nervus facialis is well developed (section 70) the shape of the degenerated area is a little different

from what it is lower in the medulla oblongata. At no level are the radicular fibres of the nervus cochlearis or the nervus vestibularis, or their terminal nuclei, implicated by the degenerated area. The striæ acusticæ of von Monakow, the striæ of Held and the corpus trapezoides largely escape. The area of degeneration with destruction of nerve fibres is sharply limited to the area on each side of the raphé, and in this area must be sought the central connections of the nervus vestibularis and none of the nervus cochlearis. The area of the nucleus of Deiters and the nucleus triangularis escape at all levels.

The central area of degeneration shows old and recent degenerative processes. All medullated nerve fibres have disappeared within it, and it is composed of proliferated neuroglia and numerous capillaries with very pronounced perivascular lymphocytic infiltration about some of the vessels, so that there is a combination of late lesions with those of a progressive nature; the process had not reached a termination at the time of death.

The nucleus triangularis on each side has lost a considerable number of nerve-cells, and those remaining are not of normal size and shape. The photograph taken from section 61 and stained with thionin is from the lateral portion of the nucleus triangularis where the nerve-cells are normally of larger size (fig. 9). The section is chosen from the level of highest development of the nucleus triangularis. The nucleus of Deiters contains very few of the large cells characteristic of this nucleus, and sections from the level of the knee of the nervus facialis are studied especially where these nuclei are best developed. The corpus pontobulbare is of normal appearance.

The area of central degeneration is much smaller at levels corresponding to the upper fibres of the nervus vestibularis and nervus facialis (section 79), and becomes very small at section 110, which is at the level of the pons where fibres of the nervus abducens leave its nucleus (fig. 10). The nucleus of each nervus facialis shows some over-development of capillaries as the late stage of encephalitis. At the upper level of the nucleus of the nervus facialis the encephalitis begins to be more diffuse in the central portion of the tegmentum; the central area of complete degeneration implicating the raphé has almost disappeared. The diffuse encephalitis in the middle portion of the tegmentum continues in varying intensity to the level of the nervus trigeminus and above it, but is more intense below the level of this nerve. The encephalitis is slight in the upper part of the pons, but becomes very pronounced at the level of the nuclei of the nervus trochlearis and the nervus oculomotorius.

The cells of the substantia nigra are numerous, but are remarkable in their loss of pigment.

The system of the nervus octavus is one of the most complex and difficult to determine in the entire central nervous system. I have not found any presentation of it as satisfactory as that of C. Winkler in his elaborate work. The radicular fibres are fairly well understood, and the central fibres of the nervus cochlearis are also known in their essential details in man, but the course of the central fibres of the nervus vestibularis in man is still very obscure.

Marburg states that it is remarkable that a tract analogous to the lemniscus or the tractus spino-tectalis et thalamicus, from the terminal nuclei of the nervus vestibularis, has not been determined with certainty. The statements of Kölliker, Held and Obersteiner, are too indefinite to permit the recognition of a secondary centripetal system. Very fine fibres go from the nucleus of Bechterew, the nucleus parvicellularis triangularis and the nucleus descendens medially in the fibræ arcuatæ and decussate in the raphé, as assumed by Freud, Kölliker, Obersteiner and Held. It is difficult to trace further the course of the cerebropetal fibres of the nervus vestibularis.

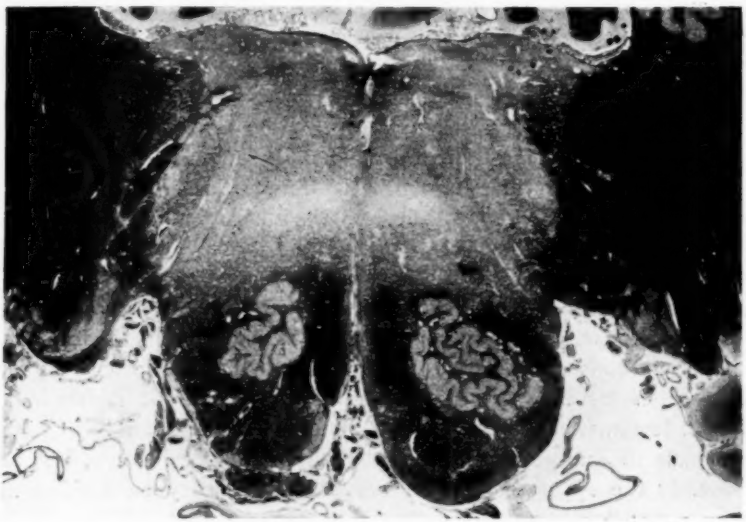


FIG. 2.—Section 33. The degeneration on each side of the raphé has united and implicated the raphé. Figs. 3, 4 and 5 are taken from parts of this section.

Winkler says that on account of the considerable development in man of the cortico-ponto-cerebellar system, and of the influence of this system on movements, and of the development of the cortico-spinal tract, the reflex system of the nervus octavus has not the importance it has in the lower types. The Deiters' spinal tract, the spinal portion of the two longitudinal fasciculi, the rubro-spinal tract and all the paths designated as accessory pyramidal tracts, have a relatively feeble development in man. It is proper to apply to man conclusions drawn

from the reflex paths of the octavus system in animals, as the parts of the system of the nervus octavus in man which are comparable to those of the higher mammals are only partially known. In man the fasciculus of Fuse forms an important union between the nucleus triangularis and the nucleus intercalatus and the tegmentum, and the nucleus intercalatus is of importance. This is almost all that we know of this portion of the system of the nervus octavus in man.

In order to obtain some idea of the central connections of the nervus octavus we are, therefore, forced to study these paths in animals, and the work of Winkler in this field has no superior.

He does not follow the usual custom of separating the nervus octavus into the nervus cochlearis with the function of audition, and the nervus vestibularis with the function of equilibration. He considers this division inexact, and believes it causes difficulty in understanding the system, and prevents the possibility of taking into consideration the reflex paths of the tractus octavo-mesencephalicus (lemniscus lateralis), which passes from the nucleus ventralis of the nervus octavus.

In the customary acceptation this tract is only one of acoustic projection, and no value is attached to the nuclei intercalated. If one admits that the nervus cochlearis conducts solely the fibres of the cochlea, one is obliged to reserve all the secondary paths from the tuberculum acusticum and the nucleus ventralis for excitations coming from the cochlea, and this is inexact. Winkler attempts to introduce a different conception. The nervus octavus is not formed by two nerves, but by as many nerves functionally different as there are distinct terminations in the labyrinth. It is not yet possible in higher mammals to indicate for each system a special localization, but provisionally the apparatus of the nervus octavus may be divided into three parts:—

(*a*) The fibres of the cochlea. They are contained in the nervus cochlearis.

(*b*) The fibres of the maculæ acusticæ, or fibres of the otolithic organs. Some of these (those of the sacculus) are in the nervus cochlearis; others (those of the utriculus) are in the nervus vestibularis.

(*c*) The fibres of the semicircular canals. These are in the nervus vestibularis.

The cochlear fibres are in part for audition; in part a reflex path for cochlear excitation.

The fibres from the otolithic organs conduct the impulses which determine the tonic reflexes of the eyes, the trunk and the limbs, on

displacement of the head in relation to the rest of the body. In collaboration with other impulses, especially kinesthetic, extero-receptive and optic, they determine the position of the different parts of the body. The impulses from the semicircular canals play a secondary rôle in the production of these tonic reflexes. They are concerned only in movements of the entire body (reactions of rotation, orientation of the eyes and of the head after rotation, &c.).

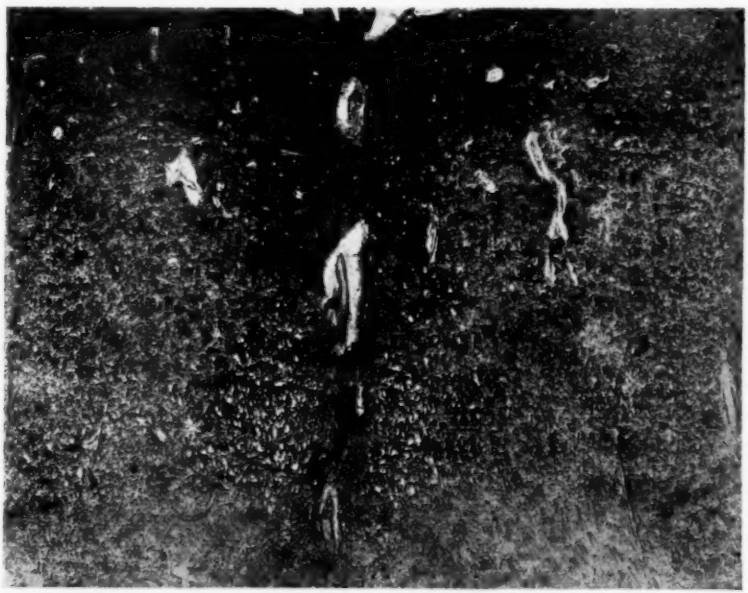


FIG. 3.—Showing fibres decussating at the posterior part of the raphé, but great destruction of the longitudinal fibres of the raphé, and no transverse fibres decussating near the area of degeneration in the lower part of the photograph.

NERVUS COCHLEARIS.

The cochlear fibres pass by the nervus cochlearis to the tuberculum acusticum and the disto-dorsal portion of the nucleus ventralis.

Secondary systems from the nucleus ventralis are three:—

(1) The corpus trapezoides arises in the nucleus ventralis. It is not such an important structure in man as in the rabbit and cat. All its associated structures are small in man, so that it must be admitted that the acoustic path of man is less important, or that there must be another path than the corpus trapezoides.

Fibres pass from the distal portion of the nucleus ventralis and the nuclei trapezoides mediales and establish a crossed and direct connection with each nucleus olivaris superior. The intervention of these nuclei establishes a new connection direct with the nucleus of the nervus abducens, and by the intermediary of the fasciculus longitudinalis posterior with the nuclei of the nervus oculomotorius. All the excitations derived from change in the position of the head can in this way be transmitted to the oculomotor nuclei, both crossed and direct.

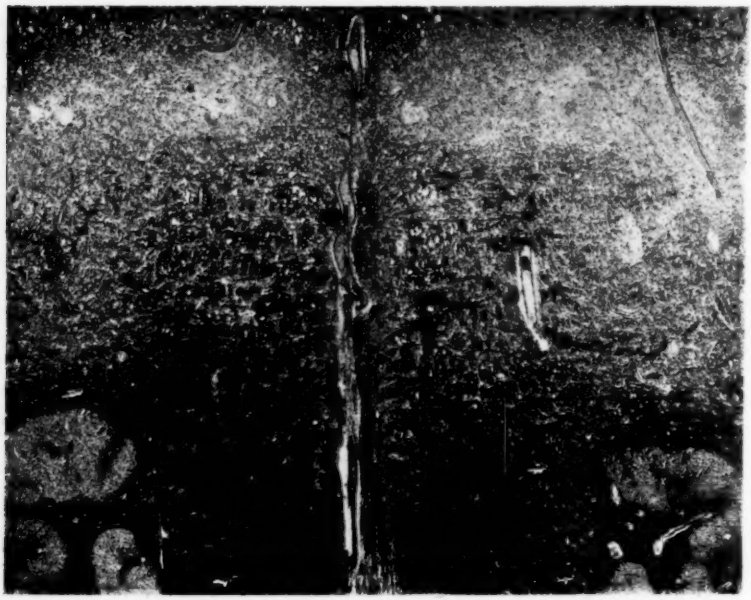


FIG. 4.—Showing transverse fibres decussating in the lower part of the photograph, but none in the area of degeneration in the upper part of the photograph. Fibres may be recognized belonging to the corpus trapezoides. Longitudinal fibres in the raphé are absent at the area of degeneration.

Accepting these statements of Winkler, and recognizing fully in man the connection of the nucleus olivaris superior with the nucleus of the nervus abducens, if we may further believe that this connection is by means of fibres from the sacculus and utriculus, we are able to understand this important pathway for the function of the otolithic organs as described above by Winkler. These pathways would be seriously implicated in the central area of degeneration in the case which forms the basis of this paper.

(2) A crossed tract passes from the disto-ventral portion of the nucleus ventralis to the two nuclei of the lemniscus lateralis, and from these nuclei there is a direct and a crossed connection for the motor column of the spinal cord by the fasciculus longitudinalis posterior. The impulses produced by changing the position of the head may be transmitted by this path to the limbs of the same and to those of the opposite side. It seems to me possible that these fibres might be

FIG. 5.—Fibres of the corpus trapezoides well preserved.

caught also in an area of degeneration implicating the centre of the tegmentum of the medulla oblongata.

(3) Fibres pass from the disto-ventral portion of the nucleus ventralis by means of the ventro-lateral fasciculus of the tractus octavo-mesencephalicus (lemniscus lateralis) to the posterior eminence of the mesencephalon.

The nucleus here influences by the tecto-reticular path and by the tecto-pontile path the two preceding reflex paths, and the tractus predorsalis passes from it to the motor columns of the spinal cord.

Striæ Acusticæ of von Monakow.

In man these fibres do not form a compact fasciculus as in the rabbit and cat.

Fibres from the nucleus ventralis and the tuberculum acusticum above the area ovalis corporis restiformis are known as the striæ acusticæ of von Monakow, and of these may be recognized:—

(1) Fibres which terminate in the most lateral portion of the nucleus triangularis. These are radicular fibres of the nervus cochlearis.

(2) Numerous fibres of the striæ which cross the nucleus triangularis and ventral to the knee of the nervus facialis pass towards the median line where they decussate. These form the greater part of the striæ acusticæ. They are principally secondary fibres from the tuberculum acusticum and the nucleus ventralis.

(3) Some fibres which pass towards a field medial to the area ovalis corporis restiformis and dorsal to the tractus spinalis nervi trigemini, known as the pars interna corporis restiformis (corpus juxtarestiforme). These fibres of the striæ acusticæ radiate between the cells of the nucleus of Deiters, but this nucleus belongs to the vestibular system.

(4) Very fine fibres which traverse the corpus juxtarestiforme and the tractus spinalis nervi trigemini curve toward the raphé, traverse the tegmentum dorsal to the nucleus olivaris superior and cross the raphé dorsal to the corpus trapezoides.

The striæ acusticæ of von Monakow occupy the dorsal portion of the tegmentum.

The Secondary Tract of Held (Striæ of Held).

This passes along the medial surface of the area ovalis corporis restiformis across the corpus juxtarestiforme, crosses the tractus spinalis nervi trigemini, turns abruptly medially and passes dorsal to the nucleus olivaris superior across the tegmentum to the raphé.

Both the striæ acusticæ of von Monakow and the striæ of Held after decussation are situated in the area dorsal to the nucleus olivaris superior, and then turn in a proximal direction and pass into the tractus medio-dorsalis of the fasciculus octavo-mesencephalicus, and continue in this fasciculus without interruption, without relation with the nuclei olivares superiores or with the nuclei of the lemniscus lateralis, to the colliculus posterior mesencephalicus, and by the brachium posticum to the ganglion geniculatum mediale.

It would seem, therefore, that in a central area of degeneration such

as I have described, the striæ of von Monakow might pass largely dorsally to the affected area and the striæ of Held ventrally to this area, and so escape destruction, and at their point of union they would be beyond the affected area.

THE FIBRES OF THE MACULÆ OR FIBRES FROM THE OTOLITHIC ORGANS.

The fibres derived from the macula sacculi are in the nervus cochlearis; the fibres derived from the macula utriculi are in the nervus vestibularis.

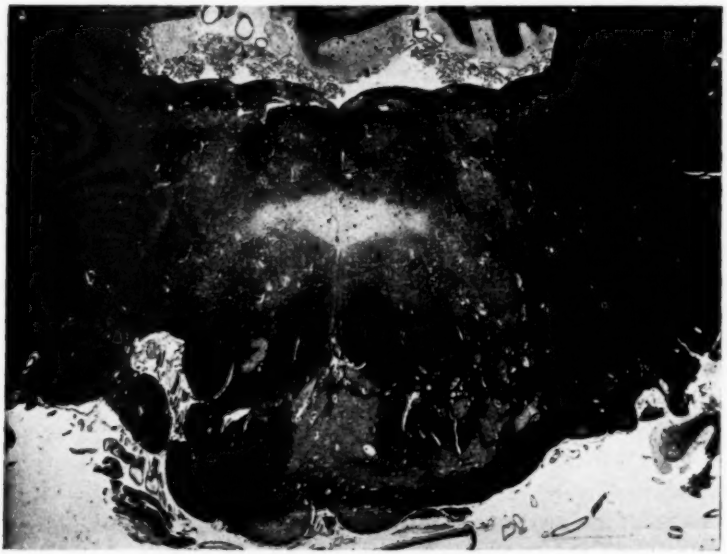


FIG. 6.—Section 70. The degenerated area destroys all fibres at the centre of the raphé.

The fibres from the sacculus go chiefly to the ventro-distal portion of the nucleus ventralis; some go by the corpus trapezoides to the nuclei trapezoides mediales; a part of the fibres from the utriculus coming from the nervus vestibularis also enter the nucleus ventralis.

Fibres from the sacculus pass also by the radiatio dorsalis nervi cochlearis, by the striæ acusticæ, to the nucleus triangularis, either directly or by a detour. After having traversed the area ovalis corporis restiformis, they enter the radix descendens nervi vestibularis. The fibres from the utriculus, which reach the radix descendens chiefly by

the nervus vestibularis, also enter the nucleus of this root and the nucleus trlangularis.

These two systems of fibres from the maculæ derive their secondary tracts from the nucleus triangularis; chiefly by the path, crossed and direct, which comes from the nucleus radicis descendentis nervi vestibularis and passes by the fasciculus longitudinalis posterior, ascending and descending, to the oculomotor nuclei and the motor column of the spinal cord.

It is also probable that efferent paths from the nucleus of Deiters function as secondary tracts for fibres coming from the maculæ.

Secondary systems of the otolithic organs from the nucleus triangularis do not continue in the tractus octavo-mesencephalicus.

From these statements of Winkler it seems reasonable to assume that the fibres of the otolithic organs, associating themselves in their secondary paths closely with those of the vestibular system, probably function as do the fibres belonging to this system.

Winkler states that the myelinization of the nervus cochlearis and of the nervus vestibularis does not occur simultaneously in the human fœtus. It begins in the nervus vestibularis and its radicular radiation in the fœtus of 23 cm. It begins earlier in this phylogenetically more ancient root than in the nervus cochlearis, in which the myelinization first appears in the fœtus of 28 cm., although when the myelinization has begun in the fibres of the radiation of the nervus vestibularis, i.e., in the fœtus of 23 cm., it may also be detected in some fibres of the radiation of the nervus cochlearis in the deep layer of the mass situated dorsally at the area ovalis corporis restiformis. In the fœtus of 28 cm. in which the myelinization of the radiation of the nervus vestibularis is accentuated, the myelinization is seen also in the medial layer of the dorsal radiation, but the nervus cochlearis still shows only partially myelinated fibres, and in the lateral layer of the dorsal radiation there is no appearance of myelin.

There is, therefore, in man a difference in the myelinization of the two sections of the radicular fibres of the nervus octavus; there is also a difference among the fibres of the nervus cochlearis. The portion first myelinated in the cochlear radiation of man corresponds in position to the fibres of the ramus saccularis in the rabbit. This is an argument for the opinion, supported also by anatomical conditions, that the nervus cochlearis contains a very recent system coming from the ganglion spirale and myelinated in the fœtus of 28 cm., associated with another system more ancient which is myelinated in the fœtus of 23 cm.

As shown by the finding revealed in the rabbit by the method of Marchi, the system which is first myelinated in man corresponds to the part of the cochlear radiation of the rabbit which does not degenerate when the distal ganglion of Scarpa escapes in extirpation of the labryinth.

It is not known definitely whether the cochlea alone is concerned with audition, or whether the macula sacculi participates in the reception

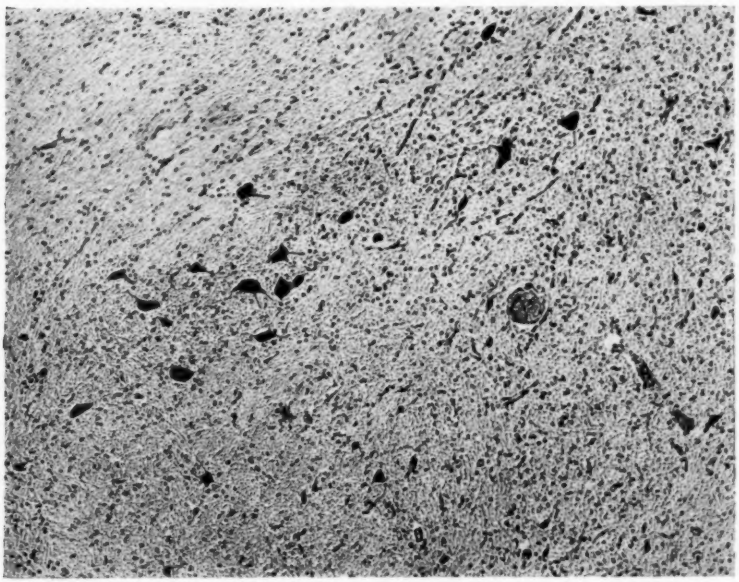


FIG. 7.—Normal nucleus of Deiters from a control specimen. No such groups of large cells are found in the degenerated nucleus of Deiters, and only an isolated cell of this type here and there is detected.

of sonorous vibrations, but it seems established that the nervus cochlearis and the ramus sacculari form together the dorsal root of the nervus octavus, and that the ramus utriculi and the rami ampulares form the nervus vestibularis.

These statements of Winkler are suggestive also that the sacculus and utriculus are part of the vestibular system, because a certain degree of similarity of function is to be attributed to fibres of a nerve distribution which are myelinated simultaneously.

The Nervus Vestibularis.

The proximal root of the nervus octavus, the nervus vestibularis, penetrates the corpus trapezoides and passes between the area corporis restiformis and the tractus spinalis nervi trigemini. This root is ventral and medial to the nervus cochlearis, and is known as the radix proximalis, or nervus vestibularis. The greater portion of its fibres pass to the nucleus triangularis.

A large number of its fibres reaching the corpus juxtarestiforme turn abruptly distally into a field ventral to the corpus juxtarestiforme and dorsal to the tractus spinalis nervi trigemini. This field can be followed downward to the commencement of the posterior columns, and is known as the tractus descendens nervi octavi; it is composed in large part by the fibres of the nervus vestibularis.

In its course distally it is accompanied by the nucleus triangularis which extends also as low as the nuclei of the posterior columns, and the fibres of the tractus descendens leave the tract at right angle to terminate in this nucleus; but within its fibres at the medial side is the nucleus tractus descendentis nervi octavi, in which its fibres also terminate.

Some fibres of the nervus vestibularis pass proximally, forming the tractus ascendens. This tract is scarcely represented in the rabbit but is much more distinct in the cat. It curves proximo-medially toward the lateral wall of the fourth ventricle; some of its fibres terminate in the nucleus of Bechterew and another portion terminates in the proximal part of the nucleus triangularis.

Winkler recognizes as primary nuclei of the nervus vestibularis the nucleus triangularis and the nucleus tractus descendentis nervi octavi. He has never succeeded, in spite of numerous attempts, in following the radicular fibres of the nervus octavus to the cerebellum or into its nuclei.

The nucleus triangularis is rightly regarded as the principal nucleus of the nervus vestibularis. This nucleus extends from the nucleus of Bechterew to the nuclei of the posterior columns. It is always accompanied by the radix descendens of the nervus vestibularis. This nucleus is rich in fine fibres derived from the radix descendens. It is traversed by fibres of different origin, as the striæ acusticæ and the tractus vestibulo-spinalis. This nucleus is largest at the knee of the nervus facialis. Some of the medium-size cells of the nucleus triangularis form a bundle to the tractus of Fuse, which puts them into relation to the

formatio reticularis. I shall have occasion further on, in speaking of the striæ acusticæ of Piccolomini, to refer to this statement.

Winkler says that some of the fibres of the nucleus triangularis enter the nucleus of Deiters or the nucleus proprius of the radix descendens; finally they pass in large number by the fibræ tegmento-cerebellares to the cerebellum. The nervus octavus does not send any fibres to the cerebellum in higher vertebrates, but its primary nuclei have considerable connections with it. Two fasciculi come from the

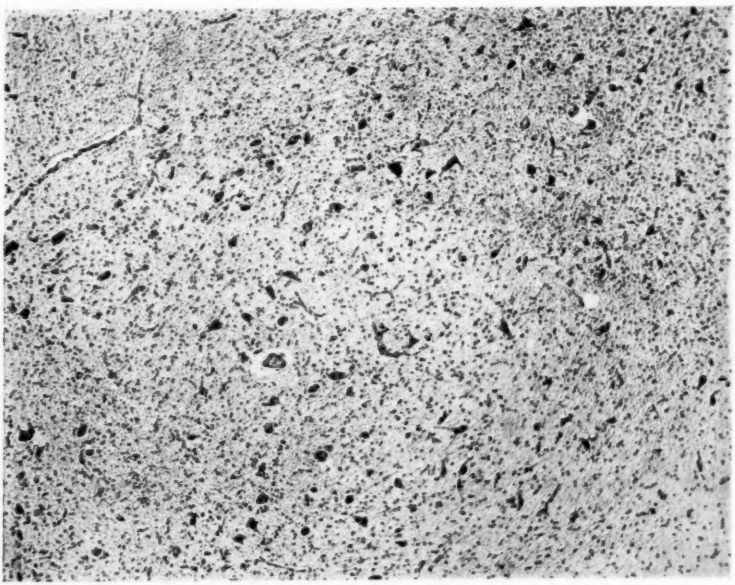


FIG. 8.—Normal nucleus triangularis for comparison with fig. 9.

nucleus triangularis: the fibræ perforantes mediales and the fibræ perforantes laterales (fibræ tegmento-cerebellares). The fibres surrounding the cells of the nucleus of Deiters and the nucleus proprius o the radix descendens come chiefly from the large cells of the nucleus triangularis.

The chief function of the cells of the nucleus triangularis is connection with the neighbouring nuclei. Long fibres come from the large cells of its ventro-lateral pole, and for this reason these cells are assigned to the nucleus proprius radicis descendentis. The cells of

the nucleus triangularis are chiefly relay cells. They have three chief connections:—

(1) With the nucleus nervi abducentis and the nucleus nervi hypoglossi.

(2) With the cells of the nucleus of Deiters and of the nucleus proprius radicis descendentis; these are connected proximally by long fibres with the nuclei nervi trochlearis and nervi oculomotorii, and distally with the medial group of the spinal cord.

(3) With cells of the cerebellar nuclei.

The nucleus of Deiters and the nucleus radicis descendentis are under the influence of the cerebellum. A considerable mass of fibres passes to the cerebellum from the nucleus triangularis. The greater part of the longitudinal fibres of the corpus juxtarestiforme degenerate toward the cerebellum; these are the fibræ perforantes corporis juxtarestiforme or fibræ tegmento-cerebellares, of which there are two layers, the fibræ laterales and the fibræ mediales.

The nucleus dentatus receives few of the fibræ tegmento-cerebellares; it and the nucleus emboliformis receive the fibræ laterales, the nucleus globosus and the nucleus fastigii receive the fibræ mediales. The nucleus fastigii and the nucleus globosus send out a fasciculus of fibres to the nucleus of Deiters and the nucleus radicis descendentis nervi vestibularis, known as the fasciculus uncinatus.

Cerebellar nuclei also send fibres to the mantle of the nucleus olivaris superior. They also send fibres through the brachium conjunctivum cerebelli to the nucleus ruber, from which is derived the tractus rubro-spinalis, which runs through the tegmentum of the medulla oblongata.

It is probable that some of these fibres were affected in the degeneration of the tegmentum I have described, as in the upper part of the pons a considerable area was involved by the encephalitis in addition to the central area of degeneration in the medulla oblongata and lower pons. Loss of vestibular function may have been in some measure caused in this manner, by implication of reflex fibres.

From the nucleus of Deiters comes the tractus vestibulo-spinalis which forms a connection with the motor cells of the spinal cord, especially with those of the cervical segments. This tract may have been implicated at least partly in our case, as it is dorsal to the nucleus olivaris.

Sachs and Alvis, in their experimental work on the nervus octavus of the dog, were unable to confirm the observations of Fraser that large

numbers of fibres from Deiters' nucleus pass up the fasciculus longitudinalis posterior. In none of their cases, however, were the lesions as large or extensive as those that Fraser produced.

Winkler speaks of the fibres coming from the nucleus of Deiters and the proximal part of the nucleus radicis descendentis as forming a considerable fasciculus, which makes a connection with the nuclei of the nervus abducens and the nervus oculomotorius by the fasciculi longitudinales posteriores. This fasciculus could hardly have escaped in our case, and to its involvement is probably due, partially, the loss of

FIG. 9.—Section 61. Photograph taken from a level corresponding as nearly as possible with fig. 8. A great difference is seen in the nervecells.

vestibular function. The nucleus of Deiters is situated proximally in the vestibular system, and receives fibres from the semicircular canals. The representation of this fasciculus in Winkler's figure 312 A of the rabbit's brain, shows the tract sufficiently far forward to be a central area of degeneration at the raphé interrupted by such as I have described.

Winkler states that the Bárány reaction of the head and eyes to rotation may be obtained in a rabbit without a cerebellum, even after

removal of the prosencephalon and thalamencephalon, i.e., in an animal with only a mesencephalon. Even without a mesencephalon, if the nucleus of Deiters is respected and the vestibulo-spinal tract functions, an animal still responds to rotation by a reversed movement of the head, effected by the musculature of the neck. The vestibulo-mesencephalic fibres must, therefore, have an important rôle in the Bárány reactions in the rabbit at least, and presumably also in man.

THE STRIÆ ACUSTICÆ (PICCOLOMINI) OF THE FOURTH VENTRICLE.

The relation of these striæ to the nervus octavus needs further study. Winkler states that the tuberculum acusticum of man differs from that of all other mammals, as at its dorso-lateral border are the fibres of the striæ medullares (acusticæ of Piccolomini), which certainly have no direct relation with the nervus octavus and no part in audition. They are distinct only in man (Fuse). Winkler believes these fibres arise in the pedunculus floccularis of the cerebellum, pass along the floor of the fourth ventricle towards the raphé, cross this, and terminate, at least partly, in the formatio reticularis of the tegmentum pontis. He thinks it is possible that these fibres pass dorso-ventrally and into the nucleus arcuatus medialis.

Schroeder van der Kolk believed the striæ medullares had no relation with audition. He found them well developed in a deaf mute and absent in a musician.

These fibres become medullated after birth, and they atrophy, according to Winkler, with destruction of the pars flocculus of the cerebellum.

Because the striæ medullares and the nucleus ponto-bulbaris are important structures in man and not in animals is no argument against their possible relationship to the vestibular system. Parts of the octavus system important in the higher mammals are less important in man. It is well at least to consider whether these structures could have a rôle in vestibular function.

Marburg states that Fuse, a pupil of von Monakow, was the first to demonstrate with certainty the relation of the striæ medullares (striæ acusticæ, striæ cerebellares, Bodenstriæ, striæ of Fuse) to the cerebellum, although Kölliker and Bechterew had assumed that this connection existed. Ziehen had employed the name striæ cerebellares for them.

Spiegel, as Kölliker had done, established a relation between these

striæ and the nuclei eminentiæ teretis, and compared these nuclei with the nuclei arcuatus, and regarded them as analogous with the pontile nuclei. He also considered the conductor sonorus as connected with the striæ medullares, and believed that a part of the medial abnormal fibres of the fourth ventricle represented a part of these striæ, which instead of passing directly from the nuclei eminentiæ teretis into the raphé, ran a short distance caudally or orally before entering the

FIG. 10.—Section 110. The central area of degeneration has greatly diminished in size at this level corresponding to the nucleus of the nervus abducens on each side.

raphé. The conductor sonorus represents a variation also of these striæ, and passes forward in the region of the brachium conjunctivum, so reaching the cerebellum, while the striæ pass into the corpus restiforme. Spiegel regarded the striæ as phylogenetically a relatively young system and not definitely established, therefore capable of variation. These fibres are very imperfect in animals.

Fuse denied a relation of these striæ to the nucleus arcuatus, but

brought them into relation with the nuclei of the substantia reticularis near the raphé. He compared these fibres with those of the middle cerebellar peduncle.

Marburg studied a case in which these striæ, on one side only, stained in a peculiar manner in Weigert preparations, and therefore could be traced. Previous studies on embryological tissue had prepared him for the conclusion that these striæ are nothing more than a bundle arising in the corpus ponto-bulbare and passing to the cerebellum. He confirms fully the findings of Essick regarding the corpus ponto-bulbare.

He says that in some cases fibres pass from the corpus ponto-bulbare ventrally, curve laterally about the nucleus olivaris and the outer part of the anterior pyramid, enter the raphé, cross to the opposite side to the floor of the fourth ventricle and probably are in part interrupted in the nuclei eminentiæ teretis, then pass on the floor of the fourth ventricle towards the corpus restiforme.

In addition to these fibres it is possible that other fibres pass from the corpus ponto-bulbare dorsally about the corpus restiforme and then appear cut off. Marburg was able to determine that some of these fibres have a course somewhat resembling that of the striæ of von Monakow, and form a part of the most dorsal of the fibræ arcuatæ internæ, then cross with these to the other side. It is possible that where these fibres appear as if cut off they merely change their direction, and after passing a little distance forward enter the striæ medullares.

A third course for fibres from the corpus ponto-bulbare is definite. Arcuate fibres pass from this nucleus with the pretrigeminal marginal fibres, or a little dorsal to these, medially. Some of these he could follow to the raphé crossing to the opposite side. Marburg places the most important part of the corpus ponto-bulbare ventral to the nucleus ventralis. He believes the striæ medullares represent a system interrupted in the corpus ponto-bulbare, which, like the pontile fibres, passes from the cerebral cortex caudally, not always in the same manner, partly by means of the fasciculus obliquus, or caudal to the pons by means of the pyramid.

Whether this system, analogous to the pontile system, has a special function or is merely ontogenetically a part of the pons, cannot be determined with certainty, but it is more probable that the latter view is correct.

Spiegel, in a paper on the nucleus funiculi teretis, quotes Fuse as

showing that degenerated fibres of the striæ acusticæ of von Monakow in man could be followed from a lesion of the lemniscus lateralis to the tuberculum acusticum, while the striæ medullares of Piccolomini were intact. It is important to study Essick's paper on the corpus ponto-bulbare.

In 1907 Essick described a ganglionic mass which can be seen overlapping the corpus restiforme just caudal to the tuberculum acusticum and forming a direct lateral process or extension of the ganglion mass of the pons. To this structure Essick gave the name of corpus ponto-bulbare. He states that it was seen long ago by Clarke, who regarded it as an aberrant strand from the striæ medullares, and it probably was seen by Arnold, who also described it as belonging to the strial system. The caudal tip was described by Retzius and Henle, but none of these observers followed the structure in cross sections, and its significance was overlooked. Essick's paper gives the first description of its whole form, and for the first time demonstrates its connection with the ganglion mass of the pons.

As he describes the corpus ponto-bulbare, it constitutes a horn-shaped process of the pons which extends caudally, wrapping around the lateral side of the corpus restiforme so as to end on its dorsal surface, forming, in part, the lateral boundary of the fourth ventricle. It can be seen making its appearance on the ventro-lateral surface of the pons near the emerging root bundles of the nervus trigeminus and extending backward, passing between the roots of the nervus octavus and the nervus facialis. Continuing backward ventral to the corpus restiforme, the main mass passes dorsal to the emerging roots of the nervus glossopharyngeus.

As soon as these caudally directed fibres leave the pons they are accompanied by a cellular mass which is itself distinct from the neighbouring structures. This nuclear mass fuses with the pons between the nervus facialis and nervus octavus, and gains the dorsal surface of the medulla oblongata by passing around the corpus restiforme caudal to the tuberculum acusticum.

There are some serious objections to considering the striæ medullares as part of the vestibular system. They are medullated much later than are fibres of the nervus vestibularis. They are insignificant in lower animals. No one has asserted that a connection exists between them and the nervus vestibularis. I have failed to find any degeneration of the cells of the corpus ponto-bulbare in the case described in this paper,

and the striæ medullares were seriously degenerated in this case. There is, however, another aspect to this question.

The fronto-ponto-cerebellar tract may be a fasciculus, according to some authorities, by which the frontal lobe exerts control over the equilibrium, and in this way may be explained the frontal ataxia of Bruns produced by tumours of the frontal lobe.

Donath says Bárány in 1913 called attention to vestibular symptoms produced by tumours of the frontal lobe. Szász and Podmanicsky, in 1917, found in injuries of the frontal brain that spontaneous past-pointing could be demonstrated in the minority of cases, but could be obtained easily by cooling off the skin with ethyl chloride. This reaction takes place through the ponto-cerebellar tract. Their observations were confirmed by Blohmke, Reichmann and Mann.

Donath in this same paper speaks of the remote effects of tumours of the frontal lobe as vestibular disturbances of equilibrium associated with nystagmus.

The corpus ponto-bulbare has the structure of the pontile nuclei and may be in connection with ponto-cerebellar fibres coming from the cerebrum; by close association with the vestibular system it is possible that it and the striæ medullares may have an important rôle in the function of this system. It is to be recalled in this connection that Winkler found fibres passing from the nucleus triangularis to the striæ medullares, and he speaks of the fasciculus of Fuse as forming an important union between the nucleus triangularis and the nucleus intercalatus and the tegmentum.

The fasciculi of the nervus octavus in its vestibular system, which possibly might be considered as injured in such a central lesion of the medulla oblongata as I have described, are :—

The tractus vestibulo-spinalis situated dorsally to the nucleus olivaris.
The tractus rubro-spinalis.

Fibres of the ramus sacculi and possibly of the ramus utriculi which pass in the corpus trapezoides to the nucleus olivaris superior, and from here form a connection with the nucleus of the nervus abducens and the nervus oculomotorius.

Fibres of similar origin which pass to the two nuclei of the lemniscus lateralis, and from these nuclei form a connection with fibres passing to the fasciculus longitudinalis posterioris for the motor column of the spinal cord, and possibly for the nuclei of the nervus abducens and the nervus oculomotorius.

Fibres from the ramus sacculi by means of the nervus cochlearis and the striæ acusticæ of von Monakow to the nucleus triangularis and the nucleus radicis nervi octavi, which form a connection with fibres from these nuclei passing to the fasciculus longitudinalis posterior and to the nuclei of the nervus oculomotorius and to the motor columns of the spinal cord.

Fibres of the ramus utriculi by means of the nervus vestibularis to the same nuclei and forming a similar connection.

Fibres of similar origin and destination by way of the nucleus of Deiters.

Reflex fibres from the primary nuclei of the nervus octavus through the cerebellar nuclei and by means of the fasciculus uncinatus and of fibres to the mantle of the nucleus olivaris superior entering the tegmentum of the medulla oblongata.

Possibly fibres of the striæ acusticæ of Piccolomini and of other fibres from the corpus ponto-bulbare passing ventrally and then into the raphé.

REFERENCES.

[1] Donath. *Journ. of Nerv. and Ment. Disease*, 1925, **61**, 113.

[2] Essick. *American Journ. of Anat.*, 1907, **7**, 119.

[3] Fuse. *Neurolog. Centralbl.*, 1912, **31**, 403.

[4] Marburg. "Handbuch der Neurologie des Ohres," Alexander and Marburg, Bd. i, Berlin, 1923.

[5] *Idem. Schweizer Archiv f. Neurol. und Psychiat.* (Festschrift für von Monakow), 1923, **13**.

[6] Sachs and Alvis. *Arch. of Neurol. and Psychiat.*, 1921, **6**, 119.

[7] Spiegel. *Jahrbücher f. Psychiatr. und Neurol.*, 1918, **38**, 220.

[8] Winkler, Cornelius. *Opera Omnia*, vol. vii, "Anatomie du système nerveux," Haarlem, 1921.

THE RELATIONS OF THE CORPUS STRIATUM AND THE PALLIUM IN VARANUS, AND A DISCUSSION OF THEIR BEARING ON BIRDS, MAMMALS AND MAN.

WILLIAM HERMAN, M.D., BOSTON.

(From the Central Institute for Brain Research, Amsterdam.)

Part I.—The Neostriatum and Archistriatum.

It is with considerable trepidation that one approaches a subject so profoundly studied by distinguished investigators as the striate complex.

The history of the approach to this problem has been thoroughly reviewed by Wilson [23], extending from the rather naive concept of Thomas Willis in 1667 to the very detailed and accurate studies of both its anatomy and physiology at the present time.

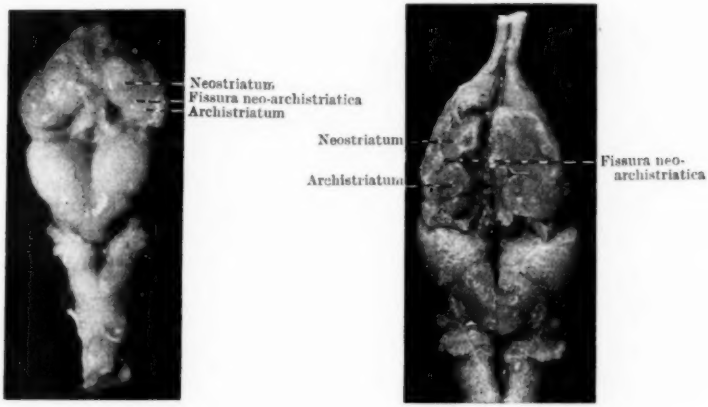
But the very multiplicity of approach and mass of work which has accumulated has led to such confusion of terminology and interpretation that there has arisen a need of simple studies on simple animals in which one can observe anatomical relationships, as they first arise in phylogenetic development in response to new adaptive needs.

Following the suggestion of Dr. C. U. Ariëns Kappers, *Varanus salvator* was the animal selected for this study.

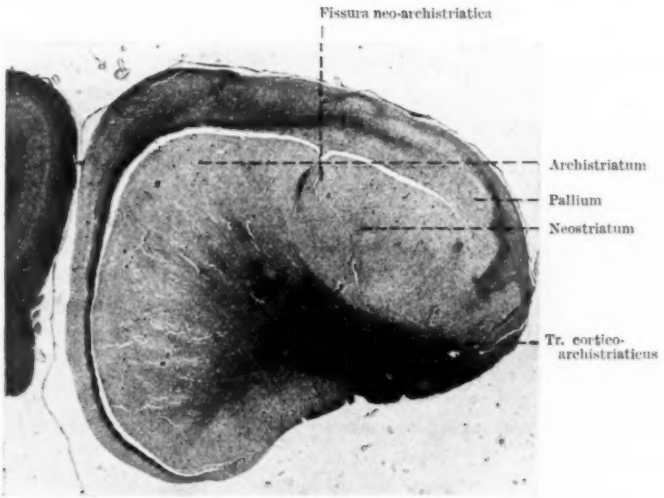
Of the reptilian series, the varanus is peculiarly suitable on account of the striking clearness of the striatal fissures, and the resulting division of the striatum into the archistriatum, neostriatum and paleostriatum.

The three components of the striatum have already been demonstrated in reptilia by Kappers [13] and de Lange [6]. These will be discussed as they appear in varanus, proceeding latero-medially in sagittal sections. Both cross and sagittal series of varanus were used, stained by the Weigert-Pal and paracarmine method as described by Kappers and Ketjen in 1911 [14].

Passing latero-medially in sagittal sections the ventricle is seen to be almost entirely filled by a mass projecting into it, and progressing medially we find that this mass of tissue is not a continuous projection, but shows dorsally a distinct fissure extending from the ventricle wall



A.—*Varanus griseus.* B.—*Tubinambis teguixin.*



C.—*Varanus salvator:* Sagittal section.

FIG. 1.—A, a photograph of *Varanus griseus*, taken at twice natural size and showing the marking off of the neostriatum from the archistriatum by the fissura neo-archistriatica; B, a photograph of *Tubinambis teguixin* taken at twice natural size, showing again the marking off of the neostriatum from the archistriatum by the fissura neo-archistriatica; C, a photograph of *Varanus salvator* cut in the sagittal plane. It shows the supra-ventricular-lying pallium and the striatum filling the ventricle. The fissura neo-archistriatica marks the neostriatum off from the archistriatum, and the tractus cortico-archistriaticus passing fan-like over the archistriatum.

into the grey substance, and marking off the mass into an anterior and posterior portion.

A similar intraventricular mass has been described by Elliot Smith [20] in sphenodon under the name of hypo-pallium, but in sphenodon the fissure which Kappers [13] has designated the fissura neo-archistriatica is not present. It is probable, according to Kappers, that the intraventricular mass in this animal is similar to that in the turtle, and represents only the archistriatum. The term fissura neo-archistriatica is used in varanus, because the fissure marks off the anterior portion of the mass, the neostriatum, from the posterior portion, the archistriatum. The neostriatum is homologous to the putamen and caudate nucleus of mammals. The archistriatum is homologous to the amygdala.

Elliot Smith has clearly demonstrated the infolding of the cortex of the pyriform lobe in sphenodon, but as in this animal there is no visible fissura neo-archistriatica, he seems to have regarded the whole striate complex as the homologue of the mammalian putamen and caudate nucleus (namely, the neostriatum) (fig. 1, A and B).

The marking off of the neostriatum from the archistriatum in varanus by the fissura neo-archistriatica is but one indication of the distinctive character of these two portions of the corpus striatum. Indeed here the first chapter in phylogenetic history of striatal differentiation in function is clearly indicated (fig. 1).

In figs. 1 and 2 a great mass of tertiary olfactory fibres is seen spreading out fan-wise in the archistriatum. None of these fibres passes anterior to the fissura neo-archistriatica. They are wholly limited to the archistriatum, and hence this tract, already described by Edinger [9], has been called by Kappers the tractus cortico-archistriaticus. Besides this I found an efferent connection running from the archistriatum and the hypothalamus, which I shall henceforth term the tractus amygdalo-hypothalamicus (fig. 5). This tract suggests a similar efferent connection of the amygdala found by von Monakow [21] in mammals (fig. 2).

Figs. 2 and 3 demonstrate the third point which I wish to stress in the distinctive character of the neo- and archistriatum. These sections are mesial to that of fig. 1, and here the great mass of fibres passing from the thalamus to the neostriatum is seen. These fibres proceed in a frontal direction and pass mesial to those of the tractus cortico-archistriaticus; the latter tract proceeds in a caudal direction.

It is evident that these two systems, which cross each other, the cortico-archistriatic and the thalamo-neostriatic, are completely distinct both in their origin and in their destination (fig. 3).

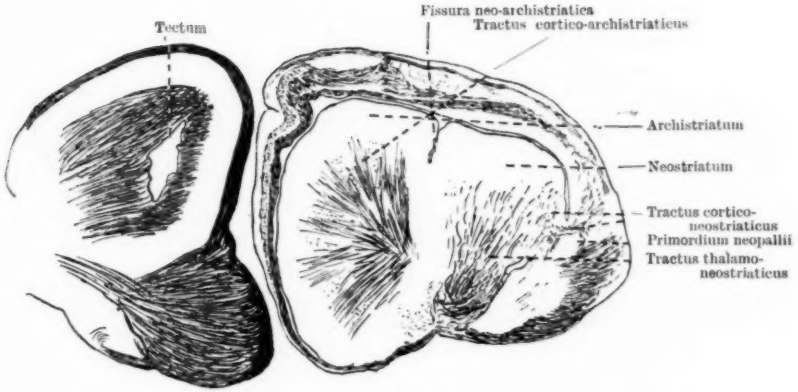


FIG. 2.—A sketch of a sagittal section of *Varanus salvator*, 100 times natural size, showing the tractus cortico-archistriaticus passing entirely to the archistriatum, and the tractus thalamo-neostriaticus passing to the ventral two-thirds of the neostriatum. The tractus cortico-neostriaticus is seen hooking under the ventricle and passing to the dorsal portion of the neostriatum. It passes under the ventricle just dorsal to the primordium neopallii.

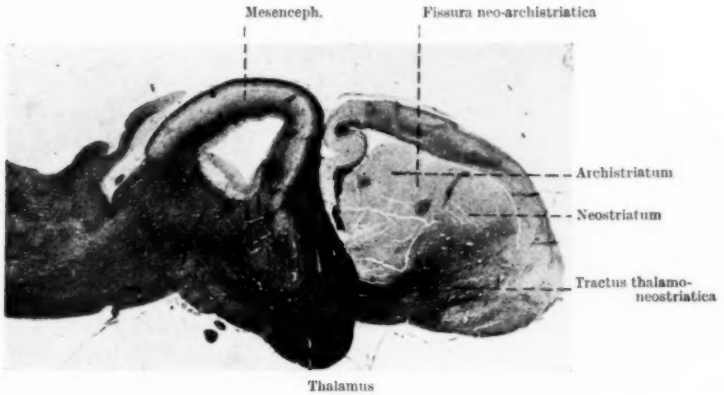


FIG. 3.—A photograph of *Varanus salvator* in sagittal section. The relation of the tractus thalamo-neostriatica to the thalamus and the neostriatum is demonstrated.

There is a fourth and very important difference between the archi- and neo-striatum. Whereas the archistriatum has an entirely pallial (latero-dorsal) origin, the neostriatum arises both from the base of the brain anterior to the paleostriatum and from the adjacent pallium (fig. 7). These facts were unmistakably demonstrated by Kappers [16] in his studies on birds and mammals. The findings in varanus are entirely in accord with them (compare fig. 7 of this paper with his figs. 7 and 15).

To recapitulate: There are four facts learned from a study of varanus, which unmistakably indicate the distinctive morphological and functional character of the neo- and the archi-striatum.

(*a*) The fissura neo-archistriatica.

(*b*) The tractus cortico-archistriatica.

(*c*) The tractus thalamo-neostriatica.

(*d*) The basal as well as pallial origin of the neostriatum in contrast to the purely pallial (lateral-dorsal) origin of the archistriatum.

There is no doubt that in their genetic relationship with the ingrowing pallium the archi- and neo-striatum have a partly common origin, as was so beautifully demonstrated by Elliot Smith in his studies of sphenodon, but in view of the findings in varanus the term hypopallium introduced by Smith [20], though suggestive from the standpoint of origin, is inadequate from the point of view of more differentiated function. Certainly in any study of reptilia, a class so fascinating because of its dramatic emergence into a strikingly new and perforce more differentiated form of existence, the attention is naturally focused on this further differentiation.

It appears clearly, in varanus, that the so-called hypopallium assumes a twofold morphological and functional character. Due to the fissuration and the large number of thalamic fibres passing anterior to the fissure, as well as the definite directing of all tertiary olfactory fibres posterior and lateral to the fissure, we are forced to consider Smith's hypopallium in varanus as a striatal complex consisting of two parts, differentiating themselves in accordance with the more differentiated life habits of the animal. The neostriatum, by its connection with the nucleus rotundus of the thalamus (mesial nucleus) and anterior thalamic nucleus co-ordinating trigeminal touch-sense with telencephalic functions, probably serves the new and highly important oral functions, whereas the archistriatum remains chiefly olfactory (fig. 5).

On the upper surface of the neostriatum a shallow fissure is next

seen in varanus (see fig. 6), penetrating a short distance into its most dorsal aspect. This fissure, which runs in an antero-posterior direction and forms a shallow groove just mesial to the lateral half of the

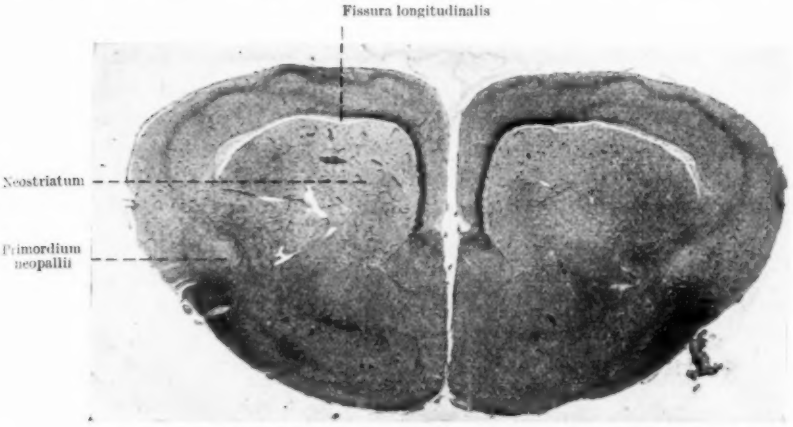


FIG. 4.—A photograph of a cross section of *Varanus salvator*, showing the neostriatum, the fissura longitudinalis indenting it, and the primordium neopallii.

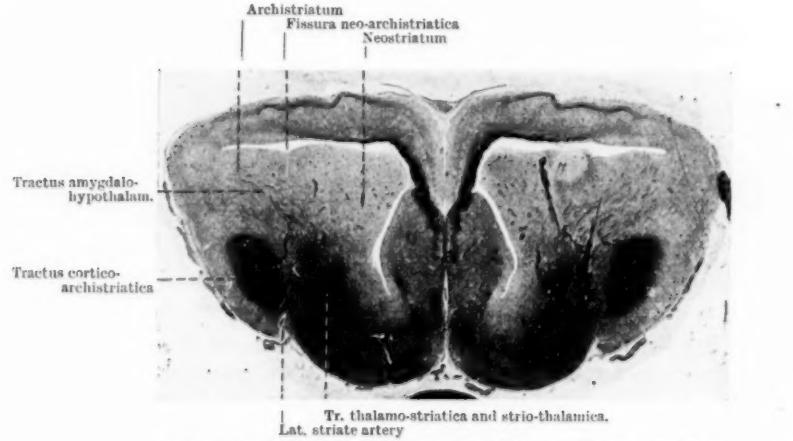


FIG. 5.—A photograph of a cross section of *Varanus salvator*. The tractus amygdalo-hypothalamicus can be seen here passing from the archistriatum into the efferent strio-thalamic radiation.

neostriatum, has been named by Kappers [15] the fissura longitudinalis. S. J. de Lange [6] first described this fissure in varanus, and suggested that it might be an evidence of differentiation of the

neostriatum into the putamen and caudate nucleus. He compared it to the fissure seen in mammalian embryos, with which, however, Kappers [15] has later shown it to be not homologous; the fissure in mammalian embryos alluded to by de Lange being the fissura neopaleostriatica of Kappers (fig. 6).

The fissura longitudinalis may be of great importance as a functional dividing line. Dr. Arthur Young, working in this Institute at present, has observed in the neostriatum of varanus, and even more distinctly in *Crocodilus porosus*, two obliquely running fibre tracts, one ending medially and the other laterally to the fissura longitudinalis, thus being apparently different in character. Similar fibre systems were observed

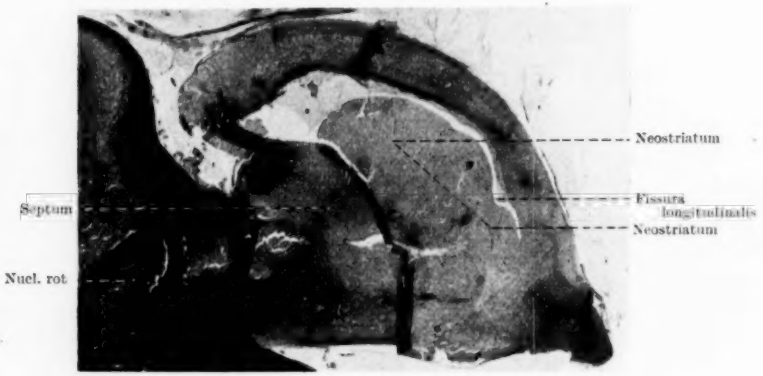


FIG. 6.—A photograph of a sagittal section of *Varanus salvator*. The fissura longitudinalis is seen marking off the neostriatum laterally by a shallow groove. The nucleus rotundus of the thalamus is here clearly visible.

by Wallenberg in birds. Kappers [15] shows in his book a diagram of the origin of these fibres based on the researches of Edinger, Wallenberg, and Schroeder, the tractus thalamo-striatalis frontalis medius arising from the anterior and dorsal nucleus of the thalamus, and the tractus thalamo-striatalis lateralis arising from the nucleus rotundus of the thalamus. The course of these tracts is similar to those in varanus, passing medially and laterally to the fissura longitudinalis. They suggest, however, no homology by their position, structure, or by the arrangement of their afferent fibre tracts to any later division into the putamen and caudate nucleus. As we know, such a division in mammals and man is entirely conditioned by the passing between the

putamen and caudate nucleus of the fibres of the internal capsule. Moreover, even in mammals the division of the putamen and caudate is more or less arbitrary, depending entirely on the varying position of the capsula interna (de Vries) [8].

The distinct direction of these two neostriatal tracts, running in an acute angle to one another, as well as their different origin, suggests a probable difference in function. The tractus lateralis, moreover, sends a few fibres to the lateral cortex, and that part of the neostriatum lying lateral to the sulcus longitudinalis may well be more related to the pallium than the portion lying mesial to the sulcus (figs. 6 and 7).

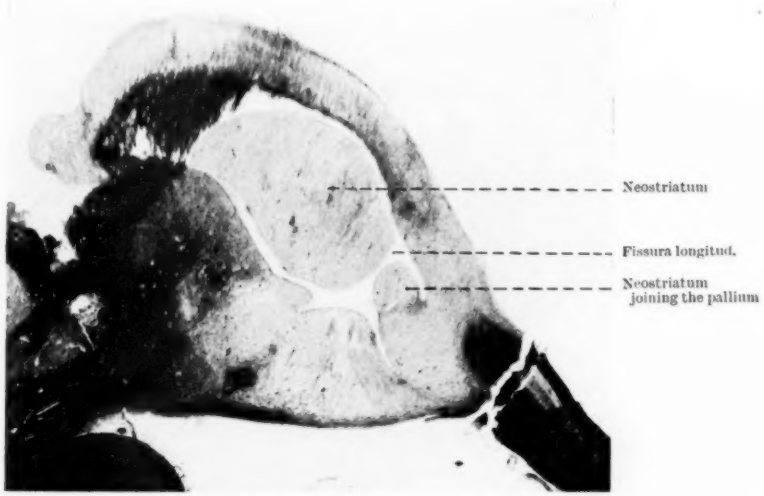


FIG. 7.—A photograph of a sagittal section of *Varanus salvator*, showing the junction of the pallium and neostriatum anterior to the fissura longitudinalis.

In varanus a fibre tract, hitherto undescribed, was seen to pass from the latero-frontal cortex into the dorsal and anterior third of the neostriatum (see figs. 8 and 9). From these two drawings it can be seen that the tract spreads like a cap from the pallium, hooking under the lateral ventricle and passing into the neostriatum. The tract is seen at the extreme lateral aspect of the hemisphere in cross sections (figs. 8 and 9) and at the extreme anterior aspect in sagittal section (fig. 9). It passes under the ventricle to enter the neostriatum, immediately dorsal to a thickening of the pallium in the lateral and

anterior wall of the hemisphere. The tract described above is an unmistakable connection between the cortex and the lateral, anterior and dorsal part of the neostriatum. We shall therefore call it the tractus-cortico-neostriaticus. It is interesting that this tract appears in varanus in an area adjacent to the formation of the primordium neopallii, and hooks under the ventricle just dorsal to this (figs. 8 and 9).

Passing a few sections medially, it becomes clear that the lateral and anterior part of the neostriatum is identical in structure with the inbending pallium (fig. 6). This fact is even more strikingly demonstrated a little further mesially, as that portion of the neostriatum which lies anterior and lateral to the fissura longitudinalis becomes distinct

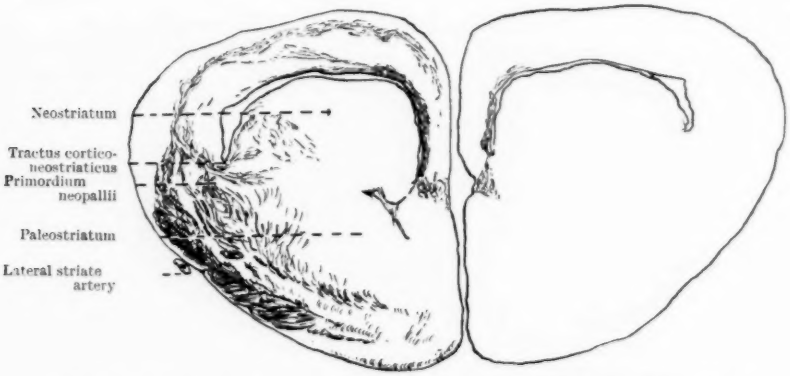


FIG. 8.—A sketch of a cross section of varanus, enlarged 100 times natural size, showing the tractus cortico-neostriaticus hooking under the ventricle just dorsal to the primordium neopallii. The lateral striate artery, one of the landmarks marking off the neostriatum from the paleostriatum, is seen here.

from the main mass of the neostriatum and fuses with the anterior pallium (figs. 7 and 9).

The presence of the tractus cortico-neostriaticus, which reveals a connection between the cortex and that portion of the neostriatum lying lateral to the fissura longitudinalis, may be another indication of the division here of the neostriatum into both a portion of purely pallial origin and one of mixed origin, pallial and basal. The question may be raised here as to whether that portion of the neostriatum arising from the pallium alone may not be homologous to the hyperstriatum superius described by Kappers in birds [16]. In this paper Kappers writes as follows: "Whether the hyperstriatum superius of birds (which arises *only* from the mantle) is included in the neostriatum in mammals or

not, cannot be settled as yet with certainty. The possibility exists that it is represented in mammals and man by the claustrum, which also is a ventricular ingrowth of the pallium (a hypopallial product in the sense of Elliot Smith, l.c.)," E. de Vries [7], in a study of mammalian and human embryos, comes to the conclusion that the ontogenetic development of the claustrum in man is quite independent of the corpus striatum, and that the origin of its cells is like that of the cortical cells. In cercopithecus, an Old-World ape, he finds that the claustrum is separated from the cortex, but joins it at the transition point of the neocortex into the lateral olfactory cortex. In guinea-pigs

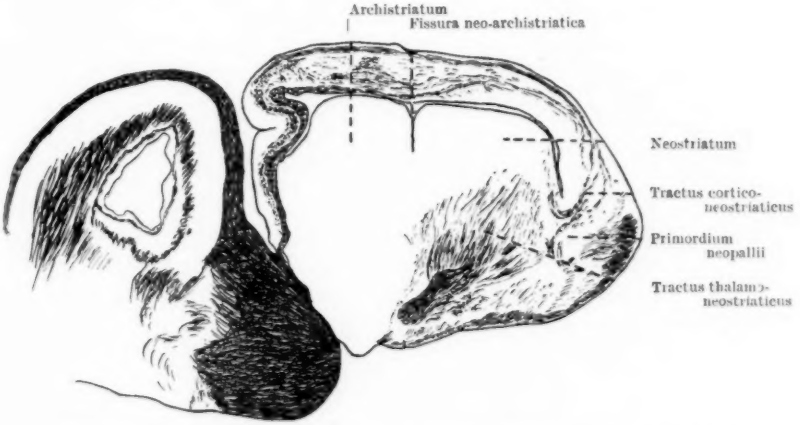


FIG. 9.—A sketch of a sagittal section of varanus, fifty times enlarged, showing the tractus cortico-neostriaticus passing into the dorsal third of the neostriatum. The tractus thalamo-neostriaticus is seen over the ventral two-thirds of the neostriatum. The tractus cortico-neostriaticus is seen passing under the ventricle to the neostriatum, just dorsal to the primordium neopallii.

during development he found that the claustrum formed a process of the deepest cortical layers of the adjacent pallium, passing from the neocortical region into the olfactory lobe and around the sulcus rhinalis lateralis. At a similar place in *Chelone midas*, Elliot Smith [20] showed in a very clear diagram the rudiment of the primordium neopallii.

Now, in varanus at an homologous point, dorsal to the fissura rhinalis anterior (see figs. 8 and 9), a similar thickening, indicating the primordial neopallium, is seen. Passing immediately dorsal to this thickening, and proceeding into the neostriatum, is the tractus cortico-neostriaticus, described above. This tract passes into the anterior and

lateral portion of the neostriatum, and never proceeds farther ventrally than its dorsal third. On the other hand, the fibres of the tractus thalamo-neostriaticus pass only to the ventral two-thirds of the neostriatum and cannot be observed in the dorsal third (see fig. 9).

It seems well to summarize here these points:—

(*a*) The afferent thalamic fibres to the neostriatum supply only its ventral two-thirds.

(*b*) The tractus cortico-neostriaticus, a connection between the cortex and neostriatum, is seen only in the dorsal third of the neostriatum.

(*c*) The fissura longitudinalis marks off the neostriatum in its dorsal or ventricular aspect, into a medial and lateral portion.

(*d*) The lateral, anterior and dorsal portions of the neostriatum are structurally identical and fused with the pallium in the region of the rudiment of the primordial neopallii.

The Paleostriatum.

As we pass further medialwards in the sagittal series, the paleostriatum, the oldest portion of the striate complex and the homologue of the globus pallidus of mammals and man, makes its appearance. This nucleus is entirely basal in origin. It is still very small, even in amphibia, but is markedly enlarged in reptilia. In birds it has become so large that it has been designated by Kappers [16] the paleostriatum augmentatum (Edinger's mesostriatum). In this memoir we will limit ourselves to the term paleostriatum.

The paleostriatum in varanus arises in the area corresponding to the tuberculum parolfactorium, at the level of the foramen of Monroe, and lies directly ventral to the neostriatum. There are three landmarks dividing the paleostriatum from the neostriatum in varanus. One is the lamina medullaris externa. This lamina, which is rich in blood-vessels, is more striking in crocodiles, but is regularly present in varanus behind and at the level of the foramen of Monroe. It was also beautifully shown by E. C. Crosby [5] in her description of *Alligator mississipiensis*, dividing her ventro-lateral area (paleostriatum) from the dorso-lateral area (neostriatum). This lamina is even more striking in birds, and Kappers [16] has found it to be here very vascular. Also John Hunter [11] in his description of the Australian kiwi observed this vascular lamina dividing the paleostriatum from the neostriatum.

A second landmark in this region is the lateral striate artery (figs. 4, 5, 8). Elliot Smith [20] demonstrated a very remarkable homology

in the position and constancy of this artery. He showed that at the place where the middle cerebral artery crosses the endorrhinal fissure, a large perforating branch is given off in the turtle's brain, which passes along the vascular boundary line between the paleo- and neo-striatum. He has also quoted the work of Ziehen and Retzius, who have shown in a large series of investigations of mammalian embryos that one or more large arteries enter the brain at the same place, namely, the postero-lateral corner of the tuberculum olfactorium, just mesial to the olfactory tract and anterior to the tubercle of the olfactory tract.

A third landmark between the paleostriatum and neostriatum in varanus is the fissura paleo-neostriatica. This fissure was first described by Kappers [16] in birds and mammals.

To recapitulate: The paleostriatum in varanus, which is homologous to the globus pallidus in man, is an entirely basal structure of large cells located in the medio-ventral portion of the striate complex. It is marked off from the neostriatum by (*a*) the lamina medullaris externa; (*b*) the lateral striate artery; (*c*) the fissura paleo-neostriatica.

The paleostriatum sends out efferent fibres by the basal forebrain peduncle, which connect the striatum with the hypothalamus and the mid-brain.

Part II.

In the preceding section I have presented a morphological description of the relation of the different portions of the striatal complex in varanus to one another, and also the relation of the neostriatum to the pallium. The finding of a new cortico-striatal connection inevitably leads to speculation on that much discussed problem in mammalian and human neurology. In addition to a brief account of experimental physiological findings, it has seemed to be of interest to give an account of certain diseases in man, showing a combined selective action on the neostriatum and cortex which is very suggestive.

Wilson [23] concludes from his degeneration experiments on *Macacus rhesus* and *sinicus* that: "no unequivocal proof of the passage of fibres, fine or medium, from either the putamen or globus pallidus to the internal capsule or crus has been obtained. The general direction of the two divisions of the ansa lenticularis is always oblique to that of the cortico-spinal fibres." From laminal lesions this investigator could trace no degenerated fibres passing by the laminæ from the corpus striatum to the cortex. He states that strio-cortical fibres are non-existent. His findings regarding cortico-striate fibres are the same.

Cajal [4] denies the presence of any cortico-striate or strio-cortical connections, as do many of the most reliable recent investigators.

On the other hand, Marinesco [18] has reported that, as a result of partial or complete destruction of the frontal lobe in dogs and apes, he could trace fine degenerated bundles of fibres passing into the striatum. This condition he found most clearly demonstrated in the caudate nucleus (neostriatum). Minkowski [19] in a recent and very important monograph has demonstrated for the first time some pre-Rolandic fibres detaching themselves from the dorsal part of the lenticulo-caudate segment of the internal capsule and passing into the dorsal part of the head of the caudate nucleus. Here they pursue a dorso-median direction, meanwhile entering into contact with the cells of the caudate nucleus as they pursue a passage of some length. He also found them in the cat after the ablation of the motor or sigmoid cortex. The same author has also reported the presence of pre-Rolandic pallidal fibres in the macaque. He believes that these fibres terminate in the grey substance of the globus pallidus (paleostriatum) and contribute to the formation of little packets of fibres, so characteristic of the globus pallidus. He also quotes from the works of Dejerine, Long and Flechsig, who found these fibres in man, and Grundstein, who reports their presence in the dog.

This is but a brief report of the investigations on this subject. Until the recent work of Minkowski, the evidence on the whole, based on the best physiological methods and technique, had failed to demonstrate conclusively any connection between the neostriatum and the cortex; but the latter's findings make us pause, particularly in view of the very striking clinico-pathological findings of which a brief summary appears below.

In 1908 Jelgersma [12], reporting a case of Huntington's chorea, found both cortical atrophy and atrophy of the head of the caudate nucleus. The caudate nucleus was reduced to one-third of its normal size and in it there was a very striking glial proliferation. Alzheimer [1] found marked changes in both the cortex and caudate nucleus, as well as a reduction in ganglion cells in the lenticular nucleus. Marie and l'Hermitte [17] reported four cases of Huntington's chorea; the cortex (especially the frontal and Rolandic regions), putamen and caudate nucleus were in all four cases profoundly affected. There was also a definite glial proliferation. The ganglion cells of the caudate nucleus were reduced to from one-fourth to one-fifth of the normal. The globus pallidus, thalamus, red nucleus and corpus subthalamicum

were also affected, but in strikingly lighter degree than the cortex and neostriatum. These two latter structures clearly bore the brunt of the disease. In a case of Huntington's chorea, recently examined by the writer at the Salpêtrière, the findings were similar to those of Marie and l'Hermitte. The selectivity of the process for the frontal and Rolandic cortex and the neostriatum was unmistakable.

Madame Vogt [22], in her monumental work on *athétose double*, in which each case was studied by serial sections, found the lesions limited to the caudate nucleus and the putamen, in which also appeared a widespread destruction of the ganglion cells (a dystrophy of the ganglion cells). The distinctive character of the lesion, however, was the thick network of medullated nerve fibres crossing the atrophic areas of the putamen and caudate nucleus. Madame Vogt suggests that this network of medullated nerve fibres is formed by the change of non-myelinated nerve fibres into medullated nerve-fibres. She feels that these fibres represent the "plaques fibro-myéliniques" found in the cerebral cortex.

L. Bouman and S. T. Bok: Senile Plaques in Cortex, Claustrum and Striatum.

No.	Names	Cortex	Claustrum	Putamen	Globus pallidus
1	H	++	+	Some well developed plaques ..	—
2	W	++	+	Thickly distributed early plaques..	—
3	Be	++	++	Many well developed plaques ..	—
4	Bo	+++	++	Many well developed plaques ..	—
5	Bl	++	++	Many well developed plaques ..	—
6	R	++	+	Many moderately developed plaques	—
7	J	+++	++	Definite early plaques	—
8	D	++	+	Early plaques	—
9	vMa	++	+	—	—
10	d V	A few early plaques	Very few early plaques	Many well developed plaques ..	—

Fig. 10.—The table reproduced here of Bouman and Bok's ten cases shows the greatest number of plaques in the cortex and claustrum in nine cases. In nine cases plaques were found in the putamen in varying degrees of development, varying from a few to large numbers. The caudate nucleus was examined in eight cases, and showed changes identical with those in the putamen. The globus pallidus in all cases contained no plaques.

In a recent contribution by Bouman and Bok [2], which gives a description of the plaque distribution in ten cases of senile dementia, striking observations are recorded. The table of their findings is reproduced here (fig. 10). It is seen that the cortex and claustrum were affected approximately in a like manner. The stage of development of the plaques was identical in both, but the number in the claustrum was slightly less. In nine cases the putamen was involved, though less than

the cortex, and in most of these nine cases the plaques were in an earlier stage of development. In one case the putamen was unaffected. In Case 10 the putamen contained many well developed plaques. In this case, on the other hand, the cortex was but slightly involved. The caudate nucleus was examined in eight cases, and showed findings exactly corresponding to the putamen. In all ten cases the globus pallidus was unaffected. The authors conclude, entirely in accordance with our own views, that these findings are valuable evidence in support of the views of Kappers on the division of the striatum in man into a paleo- or old striatum, and a new or neostriatum. The findings in the claustrum show a consistent relation between the claustrum and the cortex, and not between the claustrum and the striatum.

Of the three disease entities mentioned, two, the progressive chorea of Huntington and *athétose double* of the Vogts, are hereditary. The third, senile dementia, is degenerative. Huntington's chorea shows a definite selective action on the cortex and neostriatum. *Athétose double* is associated with lesions in the neostriatum similar to the "plaques fibro-myéliniques," seen not infrequently in the cortex. The third condition, senile dementia, limits its attack, as shown in recent studies, to the cortex, claustrum and neostriatum.

Brouwer [3], developing the earlier suggestion of Edinger, has emphasized the very significant fact that various disease processes show a marked predilection for the newer structures in phylogeny. The relative to complete escape of the globus pallidus (paleostriatum) and the profound involvement of the neostriatum and cortex in the cases cited above, is in further support of this thesis. Certainly the best physiological opinion is divided as to the existence of constant connections between the neostriatum and cortex, in mammals and man. The finding of fibre connections in an animal so low in the phylogenetic scale as a reptile should not alone serve to suggest homologous connections in man. Indeed this connection must be regarded as but a single event in a long and complex history. But when this event is combined with the findings of Minkowski in apes and the clinico-pathological reports cited above, one is constrained to believe that the subject is far from settled.

Summary of Anatomical Findings.

(1) The neostriatum in varanus, which is the homologue of the putamen and caudate nucleus in mammals, arises partly from the pallium and partly from the base, just anterior to the paleostriatum.

(2) The neostriatum receives the great thalamo-striatal tract from the anterior and medial nuclei of the thalamus. It is hence in contact with the trigeminus; and so by its pallial relations functions as a relay in the new and extremely important touch and oral sense in reptiles.

(3) In varanus a shallow fissure running fronto-caudally marks off the neostriatum at its dorso-mesial aspect into a lateral and mesial portion. A tract from the nucleus rotundus of the thalamus has been traced by Wallenberg in birds to the lateral region, and from the nucleus dorsalis of the thalamus to the mesial region. These tracts are also very clear in the crocodile. Though less distinct, they can be seen in varanus. These tracts do not reach the dorsal third of the neostriatum.

(4) There are no tracts which indicate that the fissura longitudinalis is an early division between the putamen and caudate nucleus, as certain authors suggest. These two portions of the striatum are intrinsically one and the same thing, both in structure and in function.

(5) A fibre tract passes from the pyriform cortex and hooks under the anterior and lateral aspect of the ventricle. This tract passes into the neostriatum, and does not proceed further dorsally than the ventral aspect of the dorsal third. This tract spreads forward from the lateral aspect of the hemispheres to pass like a cap under the ventricle and so enter the dorsal, anterior and lateral portion of the neostriatum. It reveals an unmistakable connection in varanus beween the cortex and the neostriatum. This tract is called tentatively the tractus cortico-neostriaticus, since we cannot state whether it is cortico-striatal or striato-cortical.

(6) A little mesial to the tractus cortico-neostriaticus, the striatal tissue lying between this tract and the ventricle is seen not only to merge with the pallium, but also to be of identical structure with it. That is to say, in varanus the most anterior and dorsal portion of the neostriatum is clearly shown to be part of the inbending pallium. This fusion takes place in the region of the rudiment of the primordium neopallii.

(7) The afferent thalamic fibres to the neostriatum supply only its ventral two-thirds, while the fibres of the tractus cortico-neostriaticus are present only in the dorsal third of the neostriatum. The tractus cortico-neostriaticus marks off the neostriatum in the lateral and anterior aspect of the brain into a dorsal portion, into which no thalamic fibres enter, and a ventral portion which receives the thalamic tract.

(8) The archistriatum, which is homologous to the amygdala in mammals, is entirely pallial in origin, and is marked off from the neostriatum by the fissura neo-archistriatica. It lies posterior and lateral to the neostriatum, and receives the great mass of tertiary olfactory fibres, forming the tractus cortico-archistriaticus. Efferent fibres were also seen passing from the archistriatum in the fore-brain peduncle to the thalamus. The exact destination of these fibres could not be determined.

(9) The paleostriatum is entirely basal in origin. It arises in the area just in front of the recessus præopticus, and lies directly ventral to the neostriatum and archistriatum. It is marked off from the neostriatum by the lamina medullaris externa, the lateral striate artery and the fissura paleo-neostriatica. The paleostriatum receives fibres from the tractus thalamo-striaticus. The efferent system of the paleostriatum runs in the basal fore-brain bundle which first appears in fishes and links the paleostriatum, by way of the hypothalamus, with the mid-brain. This tract persists throughout the vertebrate series.

In view of the connections observed in varanus, between the striatum and the pallium, a brief résumé is given of suggestive findings in certain diseases in man which have shown a selective action on the neostriatum and the cortex, as well as reports of various workers on investigations by degeneration experiments on cats, dogs and apes.

The writer wishes to express his deep gratitude to Dr. C. U. Ariëns Kappers. It was only through his constant help and suggestions, as well as the generous furnishing of his beautiful material, that this study could be made.

BIBLIOGRAPHY.

[1] Alzheimer. "Ueber die anat. Grundlage der Huntingtonschen Chorea und der choreatischen Bewegung Überhaupt," *Neurol. Centralbl.*, 1911, **30**, 891.

[2] Bouman und Bok. "Senile Plaques im Corpus striatum," *Zeitschr. f. die gesamt. Neurol. u. Psychiatr.*, 1923, **85**, 164.

[3] Brouwer, B. "The Significance of Phylogenetic and Ontogenetic Studies for the Neuropathologist," *Psychiatrische en Neurologische Bladen: Feestbundel aangeboden aan C. Winkler*, 1918, 132.

[4] Cajal. "Histologie du système nerveux de l'homme et des vertébrés," Paris, 1909.

[5] Crosby, E. C. "The Forebrain of *Alligator mississipiensis*," *Journ. of Comp. neurol.*, 1917, **27**, 325.

[6] de Lange, S. J. "Das Vorderhirn der Reptiliën," *Folia Neurobiol.*, 1911, **5**, 548.

[7] de Vries, E. "Bemerkungen über die Ontogenie und vergleichende Anatomie des Claustrums," *Folia Neurobiol.*, 1911, **4**, 481.

[8] *Idem.* "Das Corpus Striatum der Säugetiere," *Anat. Anzeiger*, 1910, **38**, 385.

[9] Edinger. "On the Importance of the Corpus Striatum and the Basal Forebrain Bundle," *Journ. of Nerv. and Ment. Diseases*, 1887, **14**, 674.

[10] *Edinger.* "Sur l'anatomie comparée du corps strié (cerveau des oiseaux)," *Compt. rend. de l'Assoc. des Anat.*, Liège, 1903, 187.

[11] HUNTER, JOHN. "The Forebrain of *Apteryx australis*," *Proceedings of the Koninklijke Akademie van Wetenschappen, Amsterdam*, **26**, Nos. 9 and 10, p. 807.

[12] JELGERSMA. "Neue anat. Befunde bei Paralysis agitans und bei chronischen Chorea," *Neurol. Centralbl.*, 1908, **27**, 995.

[13] KAPPERS, C. U. ARIËNS; and THEUNISSEN, W. F. "Phylogenese des Rhinencephalons des Corpus Striatum, und der Vorderhirn-Commissuren," *Folia Neurobiol.*, 1908, **1**, 173.

[14] KAPPERS, C. U. ARIËNS; and KETJEN, J. "Zellfärbung in Weigert-Pal Preparaten," *Zeitschr. f. wissenschaftliche mikroskopie und mikroskopische Technik*, 1911, **28**, 275.

[15] KAPPERS. "Die vergleichende Anatomie des Nervensystems der Wirbeltiere und des Menschen," Haarlem, 1921.

[16] *Idem.* "The Ontogenetic Development of the Corpus Striatum in Birds, and a Comparison with Mammals and Man," *Proceedings of the Koninklijke Akademie van Wetenschappen, Amsterdam*, 1922, **26**.

[17] MARIE et L'HERMITTE. "Les lésions de la chorée chronique progressive : la dégénération atrophique cortico-striée," *Annales de Méd.*, 1914, **1**, 18.

[18] MARINESCO. "Des connexions du corps strié avec le lobe frontal," *Compt. rend. Soc. de Biol. de Paris*, 1895, **47**, 77.

[19] MINKOWSKI. "Étude sur les connexions anatomiques des circonvolutions rolandique pariétales et frontales," *Arch. suisses de Neurol. et de Psychiat.*, 1924, **4**, 97.

[20] ELLIOT SMITH. "A Preliminary Note on the Morphology of the Corpus Striatum and the Origin of the Neopallium," *Journ. of Anat.*, 1919, **53**, 271.

[21] VON MONAKOW. "Gehirnpathologie," Hölder, Wien, 1905.

[22] VOGT, CECILE. "Syndrome du corps strié," *Journ. f. Psych. u. Neurol.*, 1912, **18**, 479, and *Neurol. Centralbl.*, 1911, **30**, 397.

[23] WILSON, S. A. K. "An Experimental Research into the Anatomy and Physiology of the Corpus Striatum," *Brain*, 1913, **36**, 427.

— —

THE NERVE-ENDINGS IN THE PANNICULUS CARNOSUS OF THE HEDGEHOG, WITH SPECIAL REFERENCE TO THE SYMPATHETIC INNERVATION OF STRIATED MUSCLE.

BY HUGH SHAW DUNN GARVEN, B.SC., M.B., CH.B.

(From the Institute of Physiology, University of Glasgow.)

I.—Introduction.

II.—Review of previous Histological Investigations.

1. On the Structure of Muscle-fibres, with Special Reference to the Existence of Two Types of Striated Fibre.
2. On the Constitution of the Muscular Nerves.
3. On Motor, Sensory, and Accessory Nerve-endings in Striated Muscle (Exclusive of Neuro-muscular Spindles).
4. On Neuro-muscular Spindles.

III.—Original Work.

1. On the Panniculus Carnosus Muscle of the Hedgehog:
   (*a*) The Muscle-fibres.
   (*b*) The Constitution of the Nerves supplying this Muscle.
   (*c*) The Motor and Accessory Nerve-endings.
   (*d*) The Neuro-muscular Spindles.
2. Note on Nerve-endings in Striated Muscle of the Frog.
3. Note on Nerve-endings in Striated Muscle of the Lizard.
4. Note on Nerve-endings in Extrinsic Eye Muscles of the Rabbit.
5. Note on Nerve-endings in Pectoral Muscles of Man.

IV.—Discussion.

V.—Conclusions.

VI.—Description of Figures.

VII.—References.

I.—Introduction.

The existence and function of the sympathetic innervation of striped muscle have been much discussed since Boeke's discovery of his accessory nerve fibres and endings. In his work on mammalian muscle, Boeke used the Bielschowsky silver method of staining nerve-fibres and neuro-fibrils, and demonstrated the presence of a medullated and a non-medullated (sympathetic) nerve supply to the individual muscle-fibres. This means a double innervation of the individual muscle-fibres, in the sense that the two nerve-fibres are of entirely different origin. Upon this foundation has been built up the theory that the cross-striped apparatus of the fibre is innervated by the somatic fibres, and is responsible for muscular movements and con-

tractile tonus, using Langelaan's distinctions, while the sarcoplasm of the fibre is innervated by the sympathetic and is responsible for plastic tonus.

This conception has recently been modified by Hunter, on the basis of Kulchitsky's histological work. Kulchitsky, using the gold chloride method of staining nerve-fibres and nerve-endings, has recently in reptilian muscle (python) described two types of nerve-endings which never occur on the same muscle-fibre. One of these is supplied by a medullated nerve-fibre and the other by a non-medullated nerve-fibre, but these two types he has never found on the same muscle-fibre. Hunter suggests that one type of muscle-fibre, innervated by somatic fibres, is responsible for muscular movements and contractile tonus, while the other type of muscle-fibre, innervated by the sympathetic, is responsible for plastic tonus. This means a double innervation of every muscle as a whole, but not of each individual muscle-fibre.

A third complication has arisen in the use of the term "double innervation," for while the traditional view has been that each muscle-fibre receives one medullated nerve-fibre, Agduhr, in recent investigations on limb muscles, has shown that each muscle-fibre is segmentally innervated. This means that the individual muscle-fibres of a muscle innervated from more than one spinal root has an end-plate from each root—that is, a double innervation in the sense that the individual muscle-fibre is supplied by two or more somatic fibres.

This short summary of the present position with its evident contradictions emphasizes the need for further detailed histological research on the neuro-muscular junction.

I regret that on the basis of my original observations I have to disagree with two of these observers, Professors Kulchitsky and Hunter, who have so suddenly been cut off in their scientific careers, and whose loss will be deeply felt in the solution of these problems.

At the outset this work was undertaken to attempt to confirm the presence of Boeke's accessory fibres and end-nets by the classical gold chloride method. Since the publication of Hunter's work various other questions have arisen in conjunction with this primary aim, and these will also be dealt with.

The first question which presents itself is the choice of a muscle for histological investigation. Mammalian muscle is preferable to reptilian or amphibian muscle, as the application of the findings must be made more especially to the function of mammalian muscle. In view of the fact that the sympathetic innervation is supposed by some

to be a tonic function, a muscle showing marked tonus, especially plastic tonus, is also preferable. For these reasons the panniculus carnosus muscle of the hedgehog—a sheet of striped muscle which lies just under the skin over its whole dorsal surface and curls the animal into a ball—was chosen. Pembrey (1903) [45] has shown that this muscle is in tonic contraction during the whole period of hibernation, and it is maintained, I presume, in its shortened condition by plastic tonus.

Some reference will also be made to some investigations on frog, lizard, rabbit and human muscle, which show several conditions of innervation which are of interest in relation to the main thesis.

I propose to review some of the previous literature on this subject under the following four headings:—

(1) On the structure of the muscle-fibres, with special reference to the general existence throughout vertebrates of two types of striped muscle-fibre.

(2) On the constitution of the motor nerves to muscle, with special reference to the size of the nerve-fibres and the existence of non-medullated fibres in the nerve before it enters the muscle.

(3) On the motor, sensory and accessory nerve-endings in muscles, with special reference to the existence of the accessory system. In reviewing this work I do not propose to cover the whole field of older investigations; it is sufficient to note that the great majority of these workers using the gold chloride method made no mention of this system of fine non-medullated fibres. However, in relation to the present investigations, those papers, in which some mention is made of non-myelinated fibres found associated with muscle-fibres, are important, and will be dealt with in more detail. The later work where these accessory fibres, or fibres like them, are described will also be dealt with in detail.

(4) On the special sensory organs in muscles—the neuro-muscular spindles.

II.—Review of Previous Histological Investigations.

(1) *On the Structure of Muscle-fibres, with Special Reference to the General Existence throughout Vertebrates of Two Types of Striped Muscle-fibres.*

The existence of two types of striped muscle-fibres in the frog has been long known. An examination of fresh frog muscle in saline shows clearly that all the muscles of the frog are composed of clear, bright,

broad fibres with very well-marked cross striation and poorly marked longitudinal striation, and of dull granular thin fibres with poorly marked cross striation and well marked longitudinal striation.

Ranvier (1817) [49] first drew attention to the marked difference in the muscles of the rabbit, the red muscles and the white muscles. Similar differences are found in the muscles of birds.

Schafer (1912) [54] noted that in other animals the distinction is not found as regards whole muscles, although it may affect individual fibres of a muscle. He quoted Klein as showing that some fibres of the diaphragm in distinction to others have a very large number of nuclei and these are embedded in protoplasm.

Grützner (1884) [29] in his paper on the two types of muscle-fibres, held that the thin granular fibres found in frog's muscle are analogous to the red fibres of the rabbit muscle, and that the broad clear fibres of frog's muscles are represented in rabbit muscle by the white fibres. He also contended that all mammalian muscles are composed of the two types of individual fibres, red and white, as the individual frog muscles are composed of thin granular fibres and broad clear fibres, the only difference being that in the mammalian muscles there are larger amounts of hæmoglobin.

The facts that in mammalian muscle there is very little difference in size in the individual fibres, that such a method as drying is necessary to show a difference in the dulness or brightness of the fibres, that the results with this method do not differentiate the two types of fibres into very clear groups and that no difference can be found with ordinary methods, seem to force one to the conclusion that the two clearly differentiated types of fibres, which appear in the frog, do not exist in this type of muscle. All that can be said definitely is that there may be fibres which contain slightly more sarcoplasm than their fellows.

Grützner did not formulate a general law of the function of the two types of fibres, but suggested that the red fibres are related to tonic contraction, and the white fibres to rapid contraction. Since he held that every muscle had varying proportions of white and red fibres, and that no muscle was completely red or white, he found it very difficult to prove definitely that the muscles having a larger proportion of red fibres showed a longer or more tonic type of contraction, or vice versa.

It is important to note that in Grützner's paper no mention is made of the muscle-fibres in the neuro-muscular spindles. These spindle muscle-fibres in mammalian muscle, at first considered to be groups of

embryonic fibres but now known to be fully developed fibres performing probably a proprioceptive function, show a marked difference from the mass of fibres in the muscle. They are thin granular fibres with well-marked longitudinal striation, and are enclosed in a laminated connective tissue sheath. In my opinion they correspond to the thin granular fibres of the frog muscle, some of which have nerve-endings upon them showing that they are rudimentary neuromuscular spindles, and they only differ from the Weissman fibres in mammalian muscle in that they are not collected in the complex neuromuscular organ, but are distributed throughout the body of the muscle between the broad, clear fibres and are not walled off by a laminated sheath.

Cilimbaris (1910) [20], in a paper on the muscle-spindles of the eye muscles, stated that in them he found great variations in the ordinary muscle-fibres such as, he remarked, one could scarcely ever find in any other part of the mammalian striated musculature. Some fibres appeared clear, were poor in sarcoplasm and had few nuclei, while others appeared dark, were rich in sarcoplasm and had many nuclei. He noted quite definitely that all intermediate stages between these two types could be seen.

Ffrangcon Roberts (1916) [51] recorded some observations on the degeneration of muscle after nerve injury, especially of the red and white muscles of the rabbit. He stated: "In striped muscle, fibres of two kinds are found, the white and the red. . . . In man each individual muscle is composed of a mixture of both kinds of fibres, while in some animals, notably the rabbit, different muscles are composed of one kind or the other, the gastrocnemius for instance being purely white, and the soleus purely red." The red fibres, he said, had more sarcoplasm than the white fibres and responded with a sluggish contraction after a long latent period, while the white fibres responded briskly. He quoted no authority for his statement regarding human muscle, nor did he advance any proof of it in his own observations.

Kahn (1924) [34] at the outset of his research on the chemical constitution of the clasping muscles of the frog at different seasons, made some histological observations which are of great interest from the point of view of the two types of muscle-fibre. In *Rana fusca* he found that the M. flexor carpi radialis was composed in the autumn and early spring of many large bright cross-striped fibres, and only a few thin sarcoplasm-rich fibres with poorly marked cross striation. These differences he found on cross-section to be shown very obviously after fixing in formol alcohol and staining with picro-fuchsin and hæmatoxylin.

In the breeding season the same muscle was examined. On cross-section the muscle appeared on first examination to show a larger number of fibres per unit area, that is, that the individual fibres were smaller in area. In the fresh preparation the preponderating number of fibres were definitely shown to be clear, large fibres as in the autumnal muscle, and a close examination of the cross-section showed that the number of small granular fibres was not increased. The appearance of a larger number of fibres per unit area was due to the fact that in the breeding season a number of fibrous filaments passing in from the sarcolemma of the large clear fibre to the central parts of the fibre gave the impression of incomplete longitudinal division of the large fibres. In the autumnal muscles the Cohnheim's areas were not well marked, but in the breeding season they were very well marked off, and in some cases the division between the groups of Cohnheim areas appeared to have the extensions of the sarcolemma mentioned above, passing in to the middle of the fibres.

These appearances Kahn thought were obviously dependent on the fact that in the breeding season there was a larger content of sarcoplasm in the large clear fibres, compared with these fibres in the autumn, for the sarcoplasm made the Cohnheim areas more obvious and the cross-section of the sarcostyle more distinct. And, most important from our point of view, he definitely stated that the richness of sarcoplasm was by no means so large in the breeding season that these fibres could be mistaken for the small granular fibres. The increased tonic activity of the muscle was therefore maintained by a change in the large clear fibres themselves and not by an increase in the number of small granular fibres.

Hunter (1925) [33] after reviewing the work of Ranvier and Grützner, said that it remains to be decided whether or not all striated muscle is composed of two types of muscle-fibre. To support his hypothesis that these two types of fibres are innervated from different sources and fulfil different functions, he brought forward first of all evidence that the two types of muscle-fibres do exist in the leg muscles of the goat and the wing muscles of the domestic fowl. In referring to this work he did not make mention of Grützner's observations that clearing agents destroy any possibility of making the differentiation, and in both the investigations on goats and birds Hunter relied mainly on the size of the fibres, which Grützner had already shown not to be a feature of the differentiation in mammalian and avian muscle.

Hunter and Royle [33] did not state whether any variation in the

size of different muscle-fibres was seen in the normal muscle of goats, but relied upon degeneration experiments to bring out the difference. They removed the lumbar sympathetic chain from one side, and after six months examined the muscle in cross-section. They found a large number of small fibres in contrast to fibres of normal size. These they stated were too numerous to be the conical ends of fibres of normal size. The endomysium between the individual fibres was increased. This experiment, in my opinion, in no way proves the existence of the two types of fibre in the normal muscle.

In the bird they stated definitely that remarkably little variation in the size of the individual fibres in the normal muscle was found, and presumably no other difference was observed, else it would have been mentioned. In his degeneration experiments the last three cervical roots, anterior and posterior, were cut without injury to the rami communicantes, and the flexors of the forearm examined in cross-section after seventy days. On section many fibres in groups were found to be of normal size or larger; other fibres, also in groups, showed a 33 per cent. decrease in size, while other groups were found with both normal and shrunken fibres. The connective tissue was increased in amount. They stated that Willard and Grau had found a progressive decrease in size, up to 68 per cent., on nerve-section. The inference therefore seems to be that the degeneration was not complete and may have affected some fibres more quickly than others. It is also worthy of note that the somatic denervation of the limb was not complete, and if Agduhr's contention is correct that muscle-fibres are themselves innervated plurisegmentally, then some of the fibres may still have had some part of their somatic innervation. If, however, the somatic denervation and degeneration were complete in those fibres showing a decrease in size, then in them degeneration was not so complete as when motor nerve-section (motor and sympathetic fibres) was performed. The intact sympathetic innervation may be held to be the cause of this less complete degeneration.

Hunter's conclusions, from his degeneration experiments, that somatic or sympathetic denervation affects some fibres and not others, and that therefore there are two types of muscle fibres mixed in mammalian or avian muscles, seems to me to require much better evidence than is afforded by these experiments.

It seems reasonable to suppose that if the two types of muscle-fibre exist together in the mass of mammalian or avian muscle, then the differentiation into the two types should be demonstrable in normal muscle, and this Hunter and Royle have not been able to show.

Bottazzi (1923) [15] said that in dogs after section of the roots of the phrenic, leaving the sympathetic fibres intact, if sufficient time had elapsed the diaphragm was almost completely degenerated on the side of section. He made no mention of histological investigation, but presumably no irregularity in the degeneration was noted.

(2) *On the Constitution of Motor Nerves to Muscle.*

One of the great difficulties that presents itself in reviewing much of the earlier work on the innervation of striped muscle lies in the fact that so very often when non-medullated fibres are figured or described they can only be followed and are described for very short distances, just proximal to their end-plates or terminations. The question at once arises: are those non-medullated fibres simply branches of the medullated fibres proximal to this point, or are they non-medullated throughout their whole course, and if so, are they to be found in the motor nerve before it enters the muscle?

Sherrington (1894) [55] made a very extensive study of the constitution of the muscular nerves and the function of the different fibres contained in these nerves. Some of his conclusions are of interest. One-third or one-half of the nerve-fibres in a nerve to a muscle are sensory, and the smallest of the myelinated fibres are for the most part, if not entirely, also sensory. These nerves contain no myelinated fibres of sympathetic origin, but do contain a number of non-myelinated fibres of sympathetic origin. Some of these non-myelinated fibres are of larger diameter than the small myelinated fibres.

Ranson (1911) [48] has shown with the silver impregnation method that the spinal nerves and posterior roots contain a very large number of deeply stained fibres which are non-myelinated, arise in part from the small ganglion cells of the spinal ganglion, and are afferent in function since they are too numerous to be entirely sympathetic.

Langley (1922) [40], in his paper on the constitution of nerve-roots, muscular nerves and cutaneous nerves, found with the osmic acid method very few non-medullated fibres in the nerve-roots and suggested that Ranson's fibres were really fine medullated fibres. In comparing muscular and cutaneous nerves, a point which is of special interest regarding the sympathetic innervation of striated muscle, Langley found that the nerves to skeletal muscle contain very few non-medullated fibres, whereas the cutaneous nerves show many non-medullated fibres. He even went so far as to say that his results

were not in favour of any considerable connection of non-medullated nerve-fibres with striped muscle-fibres. He also brought out the point that a large factor in determining the size of the nerve-fibre is the nature of the tissue with which it was connected.

Sherrington (1894) [55] had already shown that most of the larger medullated fibres in a muscular nerve are sensory in function, ending in the neuro-muscular spindles.

It is only necessary to note at this point that it is very doubtful whether the osmic acid method would enable such thin nerve-fibrils as those described by Perroncito (1902) [47], to show sufficient contrast to the connective tissue as would enable one to distinguish and enumerate them.

(3) *On the Motor, Sensory and Accessory Nerve-endings in Striped Muscle, exclusive of the Neuro-muscular Spindle-endings.*

In all previous work the gold chloride method had been chiefly used. Boeke (1909) [7] first used the silver impregnation method of Bielschowsky in his work on the development, form and connection with the muscle-fibre of the motor end-plate. His work, therefore, is unlike the older work in that his material was sectioned, not teased, and then examined.

The appearance of the motor end-plate of the reptilian muscle and mammalian muscle which he examined was strikingly different from the appearance with the gold chloride or methylene blue method. The myelinated nerve, proximal to its termination, showed the axon cylinder as a collection of neuro-fibrils closely packed together and passing into the end-plate without the characteristic narrowing seen in the gold chloride preparations. The form of the end ramifications is also very different. Instead of the very fine branches ending in deeply-stained knob- or button-like structures, he found a very complicated network of neuro-fibrils, with a great deal of anastomosis between the fibrils, and some of the neuro-fibrils passed out from the network to form simple end-loops and more complicated end-nets with anastomosing fibrils filling up the enclosed loops. The nuclei of the granular sole-plate were very clearly shown. In his sli des showing profile or transverse cross-sections, he clearly demonstrated the hypolemmal position of the plates. This method has, therefore, the great advantage that the structure of the plate is not obscured, as it is in the gold chloride method, with very darkly-stained knob-like structures, and the exact position of the termination of any fine non-myelinated fibre accompanying a myelinated fibre can be clearly visible.

In this paper also Boeke described his periterminal network. In this short survey I shall use the account he gave in a lecture in London University (1921) [11]. Here he stated that he thought the neuro-fibrils the actual conductors of nerve impulses, but that up to the present they could not be traced in the end-plates further than the granular sarcoplasm of the sole-plate. In amphioxus he showed what appeared to be direct connection of the neuro-fibrils with the anisotropous discs of the sarcostyles. In other vertebrates he described in well-stained Bielschowsky preparations a fine reticulum in the sarcoplasm, joining up with the neuro-fibrillar network. This he called the periterminal network, and thought it to be the anatomical basis of Langley's receptive substance. This periterminal protoplasmic network seemed to pass to the anisotropous discs of the sarcostyles.

The periterminal network he also found in connection with his accessory end-plates now to be described.

In April, 1909, Boeke [6] first described his system of accessory non-myelinated fibres in striped muscle. In October, 1909 [7], he elaborated his statements about them. After reviewing the work of Perroncito, Huber and De Witt, Ruffini, Crevatin, Grabower and Gemelli, he concluded that the existence of accessory non-myelinated fibres passing into motor end-plates could not be substantiated from their investigations.

In the muscle of the developing talpa, human embryo, young mouse and adult lizard, he found very fine non-myelinated fibres, passing either with the myelinated fibre, or by some other course into the end-plate and there forming little end-rings or end-nets. These fibres he never found to have any connections with the branches of the myelinated fibres, either inside the plate or outside the plate. In some cases the accessory end net or ring was completely separate from the motor end-plate on a granular sole of its own. Transitional stages between this separate accessory ending and the well-known motor ending he never found. That they were hypolemmal he definitely demonstrated, and considered them of motor function. Here he first suggested the sympathetic origin of these fibres, and a trophic or tonic function of them. He left it an open question whether they were identical with the Perroncito-Gemelli fibres or not.

In 1910 Boeke [8] in a short note referred to the work of Botezat on avian muscle, but was not convinced of the independence of the fibres described by this worker. Boeke found his accessory fibres and end-plates in the pectoral muscles of the starling (*Sturnus*). It is most

interesting, in view of Hunter's hypothesis of the two types of muscle fibre, that Boeke's figures of the pectoral muscles of the bird show definitely the accessory ending on the same muscle-fibre as the motor plate, as he had demonstrated elsewhere. The hypolemmal position of these accessory endings, Boeke maintained, made it quite easy to distinguish them from the "atypical motor endings" of Retzius, which Huber showed to be epilemmal and regarded them as sensory.

Boeke [9], again in 1913, reviewed the question of the identity of the Perroncito-Gemelli fibres with his accessory fibres. He had been unable with the gold chloride and methylene-blue methods in lizard muscle to demonstrate any connection between the fine fibre accompanying the medullated fibre and the end-ramifications of the large fibre. With the Bielschowsky method he had never seen a connection of this sort. He gave then a number of points in which his accessory fibres differed from the Perroncito-Gemelli fibres. This is of special interest in relation to confirmation of Boeke's results with the gold chloride method which I have attempted.

(1) The accessory fibres are single in the majority of cases, while Perroncito figures many instances where there are two or more.

(2) The accessory fibres do not run inside but outside the sheath of Henle, and often enter the plate from a different direction from the medullated fibre.

(3) The accessory fibres never have connections with the end-ramifications of medullated fibres in the motor-plate, but end in quite independent end rings and nets; this is true for all his specimens of both young and adult muscle.

(4) While the form of the Rouget plate varies considerably, both in individual muscles and animals, the end net or ring of the accessory fibres remains remarkably constant in form. This form he states is very like the endings in smooth muscle cells.

(5) The endings of accessory fibres are found, unlike the Perroncito-Gemelli fibres, in separate sole-plates of their own, quite removed from the Rouget plates. These are not the ultraterminal fibres (branches of medullated fibres), although Boeke also occasionally saw this type of fibre.

(6) The independence of the accessory system is conclusively proved by degeneration methods after section of the somatic fibres. In the eye muscles after section of the nerve close to the brain-stem only the remains of myelinated fibres were found, but the accessory fibres were intact. So far as Boeke was aware this had never been attempted for

the Perroncito-Gemelli fibres. From this result, Boeke claims that his thin fibres may be of sympathetic or autonomic origin.

In a further account of degeneration results Boeke (1916-17) [10] described experiments on the eye muscles which have given rise to a great deal of criticism. The third nerve was cut close to the brain-stem, and three to five days allowed for the myelinated fibres to degenerate. By Bielschowsky's method the accessory fibres and their end-plates in the eye muscles were not found to have degenerated but were normal in appearance. Again after three weeks the muscles were examined. Boeke found that a great many of the accessory fibres and endings had now disappeared. This last finding is the one subjected to criticism. Boeke's conclusion from his experiments was that these thin fibres which degenerated after three weeks were cranial autonomic, and those which did not degenerate were sympathetic fibres entering the muscle by way of the carotid artery. In converse experiments, after removal of the superior cervical ganglion, Boeke thought that the number of accessory fibres was less than normal.

With Dusser de Barenne, Boeke [12] in 1919 described experiments in the cat, where the sixth, seventh, eighth and ninth anterior and posterior spinal roots were cut inside the dura and the muscle of the seventh intercostal space examined one month later. The staining gave excellent results. No trace of the degenerated neuro-fibrils of the myelinated fibres could be seen; but fine non-myelinated fibres were found quite intact, with end nets and rings, occurring either at the end of the fibres or on fine side branches. In some cases the ending was more complex, with a number of end-nets close to one another, but this was always much more delicately built than the Rouget end-plate. Granular sole-plates and collections of nuclei suggested their hypolemmal position. These results were exactly similar to Boeke's eye experiments.

They state that while after three to four days all medullated motor terminations have disappeared, it is possible to find seemingly intact non-myelinated fibres in the cut nerves up to fourteen days. But after a month all myelinated and non-myelinated fibres in the cut nerve have disappeared, so they conclude that the non-myelinated fibres found intact after a month have a different origin—namely, sympathetic.

Botezat (1910) [17] stated that in 1906 [16], working on the muscles of birds and using the Golgi method, he found thin non-myelinated fibres passing with the myelinated fibres to have endings on the muscle-fibre. These he thought were hypolemmal and often occurred

in connection with the motor-plate, showing clearly that they were found on the same muscle-fibre. From his figures it is not definitely clear whether he was dealing with a separate set of fibres, or in some cases with collateral fibres, merely branches of the medullated fibres.

Agduhr (1918) [3] cut all the spinal roots forming the cervical plexus in the cat proximal to the rami communicantes, and found after periods of five to ten days in the interossei muscles remains of medullated fibres or their sheaths, and a large number of intact non-myelinated fibres. These he therefore believed to be sympathetic and post-ganglionic. These fibres ended in small simple end-loops in many cases, and were found on the muscle-fibres in the region of the myelinated plates, or, more commonly, distant from these, and also on the muscle-fibres of neuro-muscular spindles. The majority of the sympathetic endings he thought hypolemmal, though some he thought were epilemmal. Among the sympathetic plates he found examples which occurred away from the site of Rouget plates and which had a large extension on the muscle-fibre, composed of branches ending in end-loops, more like the motor-plates, but distinguishable from them by their delicacy. He shows an example of a single muscle-fibre having a degenerated Rouget plate and an intact sympathetic plate.

Agduhr (1919) [4] described a histo-experimental study which he made in an attempt to confirm several interesting suggestions that arose from a previous experimental study. In this earlier work he found that if maximal stimulations are given to two spinal nerve-roots supplying a single muscle, and measurement made of the force of contraction, this force is always less than the sum of the contraction forces when the roots are stimulated separately. This immediately suggested to him an overlapping in the muscle of the two spinal innervations, and pointed to the same muscle-fibre being pluri-segmentally innervated.

He chose such a muscle in the cat or rabbit as the M. flexor digitorum sublimis, which is innervated mainly from the eighth cervical and first thoracic spinal roots, and slightly also from the seventh cervical. Two of the roots were then cut at different times and allowed to degenerate while one was left intact. In this way he found the appropriate lengths of time necessary for degeneration, so that the fibres from the different roots showed either a marked degeneration, a definitely less-marked degeneration, or were normal. In this way he found a number of muscle-fibres to have two end-plates, one in either stage of degeneration and one normal. Thus the M. flexor digitorum sublimis contains a large number of individual muscle-fibres having end-plates derived from

the eighth cervical and first thoracic roots, and a few muscle-fibres having end-plates from the seventh and eighth cervical roots. In some cases he found a single muscle-fibre with three end-plates respectively from the seventh and eighth cervical and first thoracic roots.

In this way he seems to prove conclusively that for the limb muscles at least the time-honoured view of one motor end-plate on each muscle-fibre does not hold good, but that a very large number of the muscle-fibres are individually pluri-segmentally innervated. Only one argument, it seems to me, can be brought against his experiments, and that is that the proof would have been more conclusive if the anterior roots alone had been cut, so that possible sensory terminations on the ordinary muscle fibres would have been left intact. He however seems to show a hypolemmal position for all his plates by an accumulation of sarcoplasm and nuclei at the site of the degenerating plate. It is of interest that he shows no muscle-fibres with two plates in the same stage of degeneration, or two normal plates. He thought the flexor muscles contained more pluri-segmentally innervated fibres than the extensors, but could not be definite on this point.

Kulchitsky (1924) [35], using Ranvier's gold chloride method, carried out an investigation of the nerve-endings in the muscles of the snake (python). He described two types of terminations: type I, the usual Rouget end-plate formed from a myelinated nerve, and type II, an elongated simpler form, the "terminaisons-en-grappes" of the older workers, formed from a non-myelinated nerve-fibre. These two systems Kulchitsky maintained were entirely separate.

Endings of type I were compactly built and were typical Rouget plates with a well-marked granular sole-plate and hypolemmal position. The entering fibres he described as always myelinated. He could find no other system of fibres in or near the end-plates of this type, such as Perroncito described, and thought that in snakes it did not exist. The ultra-terminal fibre of Ruffini and Perroncito he regarded from his material as simply a collateral branch of the myelinated fibre which forms a small plate near the Rouget, and more rarely on a neighbouring fibre. It is unfortunate that in his fig. 9 he called one of these collateral plates an "accessory" motor-plate, using the term in an entirely different sense from Boeke. On this question of the ultra-terminal fibre, he wrote, doubtless with reliable information, "It is interesting that the authors (Perroncito, Boeke) who formerly confirmed the existence of ultra-terminal fibres as normal, at the present time consider them as only rare exceptions."

The endings of type II were usually elongated and were constantly formed from non-myelinated fibres. Tschiriew, in his original paper on these "terminaisons-en-grappes," and others had described intermediate forms between these and the Rouget plates, but Kulchitsky definitely stated that he never saw any of these transitional forms. It is perhaps unfortunate, in view of the older idea that these "en-grappes" endings were developmental forms, that Kulchitsky did not state whether his material was adult or not. I have had the pleasure of examining some of his specimens, and they do very forcibly suggest an entirely different origin for the two types, I and II. The position of type II, hypolemmal or epilemmal, was, he stated, as yet doubtful, but thought it probably epilemmal. He, in spite of this fact, maintained that they were motor-endings.

The thin non-myelinated fibres never showed any sign of being branches of the medullated fibres, but formed a plexus in the endomysium where they ended in free terminations, and in the muscle where they formed the endings of type II. In connection with this system, he found a number of small unipolar ganglion cells, with short single processes both branches of which appeared to be non-myelinated. In one case, fig. 12, he showed a ganglion cell actually in relation to an ending of type II. The great differences from the myelinated fibres made Kulchitsky suggest that this second system, with its "en-grappes" endings, is of sympathetic nature.

In relation to Boeke's work, it is of great interest that Kulchitsky stated very definitely that the two types of nerve-ending never were found on the same muscle-fibre. He, however, made no statement concerning the existence of two types of muscular fibre, as did Hunter. From his figs. 7 and 8 it would appear as though the endings of type II are found on muscle-fibres whose diameter is smaller than those having endings of type I. On this fact Kulchitsky makes no comment, and his fig. 9 does not show this difference so markedly.

In a later paper Kulchitsky (1924) [36] made observations on the nerve-endings of the frog, using the methylene blue method in conjunction with the gold chloride method. He described three types of nerve-fibre: (*a*) myelinated fibres which often lost their myelin sheaths before termination; (*b*) non-myelinated fibres; some of these were branches from myelinated fibres usually at nodes of Ranvier, while others were distinctly non-myelinated for a long course, formed plexuses and were, according to Kulchitsky, of cerebro-spinal origin also; (*c*) non-myelinated nerve-fibres of the sympathetic system. This

last group of fibres and their endings are not dealt with in this paper, but were to be communicated in a subsequent paper.

The motor terminations he held to be hypolemmal and the sensory epilemmal. He described a thin plasmatic layer enclosing the axons entering the muscle and suggested that it was analogous to the granular sole of the lizards, birds and mammals. Again he insisted emphatically that each muscle-fibre received only one motor-ending. The "atypical endings" of Retzius he stated were sensory in nature, as Huber [31] first maintained. The non-myelinated fibres as well as the myelinated formed the sensory endings of the terminal threads with leaf-like expansions. These endings were sometimes quite simple, two or three expansions, or sometimes much more complicated, suggesting an end-plate. Several of these sensory endings could be found on one muscle-fibre as others had described. He thought it possible that the sensory terminal threads also had a plasmatic layer. Some of the non-myelinated fibres he found to end in the connective tissue of the muscle.

In view of Hunter's theory it is unfortunate that Kulchitsky made no reference to the thin granular muscle-fibres which do undoubtedly exist in the frog, nor to the nerve terminations which could be found on these thin muscle-fibres.

A note of comment must be made on the different views which Kulchitsky expresses in his two papers. In one he maintains the epilemmal situation to be characteristic of sensory endings, but in the other he maintains his type II to be motor. Again a number of his non-myelinated fibres in the frog are not seen over a long distance to have connections with the myelinated fibres and are classed as cerebro-spinal sensory fibres, while in the snake the non-myelinated system, also ending in epilemmal endings, is classed as motor sympathetic fibres.

Dart (1924) [21], in a paper on the double innervation of striped muscle based in part on the examination of Kulchitsky's specimens, made a number of statements which cannot be borne out by Kulchitsky's own description. He stated that one muscle-fibre received several endings of different types, and that the so-called non-myelinated fibres could be divided into two categories: (1) absolutely non-myelinated, ending in "terminaisons-en-grappes," which he considered sympathetic sensory; and (2) finely myelinated fibres ending in small plates like myelinated plates but without any granular substance, which he considered sympathetic-motor. These observations, completely at variance with Kulchitsky's, make it difficult to lay any weight on them,

and while his scheme of the various connections of the sympathetic fibres is interesting, too many points in it yet need confirmation to warrant its acceptance.

Kuntz and Korper (1924) [37] made an attempt to confirm some of Boeke's degeneration experiments. In their control material they were successful in finding Boeke's accessory fibres and end-nets with the pyridine silver method and, for the first time, with the gold chloride method. They do not give details of the gold chloride specimens as to how far they were like those of the silver method. Four weeks after section of the seventh, eighth and ninth thoracic nerves proximal to the rami communicantes they examined the eighth intercostal muscle in dogs and found degenerated myelinated fibres, but Boeke's accessory fibres and end-nets intact. In another dog the mandibular nerve was cut intracranially and the masseter and pterygoid muscles examined, where the same results were found. Boeke's results were therefore confirmed for the first time by the gold chloride method. While no specific mention is made of the fact that the accessory endings were found on the same fibre, such may, I think, be presumed, as such a wide difference as the two types of endings being on different muscle-fibres would have been mentioned, if such had been the case.

Hunter (1924) [33] stated at the beginning of his review of the histological work on sympathetic endings in muscle, that Grützner's theory must be substantiated by some muscle-fibres having a medullated nerve supply and other fibres only a non-medullated. He accepted Kulchitsky's view that medullated and non-medullated fibres never ended on the same muscle-fibre, and also that the non-myelinated fibres ending in the "terminaisons-en-grappes" were of sympathetic origin. This was an entirely new view of their origin, and it seems to me in view of Hunter's widespread application of this work, that two points must be kept in mind; firstly, that this work was done on snake muscle and not on mammalian, and secondly, that *no* degeneration experiments were made to prove the sympathetic nature of the fibres. Hunter quoted Tschiriew and Perroncito in support of the "terminaisons-en-grappes" being on different muscle-fibres from the Rouget plates; they, however, did not look upon them as being sympathetic endings.

Of Boeke's work Hunter gave a very severe criticism. The fact however remains, that Boeke attempted and proved to his satisfaction by degeneration methods that his system of fibres was of sympathetic origin, while no degeneration experiments have yet been published in proof of Hunter's contention. Hunter cited Boeke's experiment of

cutting one of the nerves to the extrinsic muscles of the eye close to the brain-stem and examining the muscle after periods of three to five days and three weeks. The difference in the number of accessory fibres found —large numbers after three to four days, and relatively few after three weeks—Boeke explained by saying that after the short period both sympathetic and cranial autonomic fibres were present, and that after three weeks only the sympathetic fibres were present. This is open to criticism, as where could the autonomic fibres have been cut off from their ganglion cells by his operation? Wilson (1921) [58] suggested that after a short period (three to five days) of degeneration some of the thin fibres were really the myelinated fibres which had slowly degenerated and lost their myelin. This objection must carry a certain amount of weight. The whole question of the eye muscles is complicated by the fact that there are very numerous small endings of the type described by Retzius and shown by Huber to be sensory in nature. This may lead to some confusion in the interpretation of results, but it is important that Agduhr found that the sensory fibres in the limb muscles degenerate more quickly than the motor-fibres, and by analogy it seems probable that these sensory fibres in the eye-muscles would also degenerate more quickly and therefore would not complicate the question so much as might be expected. Hunter stated "that the anomalies in Boeke's interpretation of the accessory system undermine his contention that every individual muscle-fibre receives both a sympathetic and somatic ending."

It seems to me possible to explain the differences obtained after a short and longer period of degeneration in another way. Presuming that the staining of the two lots of material was equally good, the existence of fewer accessory fibres after three weeks may be due to the fact that with the inactivity of the muscle some atrophy of the sympathetic fibres may take place, not on account of their being cut off from their nerve cells but simply due to the inactivity of the muscle.

Boeke's converse experiment of excising the superior cervical ganglion, Hunter stated, did not establish the fact that all the accessory fibres were sympathetic. It is true that Boeke did not find the whole system to disappear, but only thought them fewer in number. This, it seems to me, is all that could be expected in such a complicated plexus of fibres, where connections are found with the perivascular plexus, and where the existence of some small ganglion cells peripheral to the superior cervical ganglion may yet be demonstrated.

The intercostal experiments appear to me to afford a much easier field of investigation, and here the sympathetic nature of the accessory fibres seems to have been definitely proved. Hunter, however, advances the objection that this is only proven for the muscle as a whole, and not for the individual fibres of the muscle. The period of degeneration (one month) makes it impossible to show the double innervation of each fibre, but as Boeke had already demonstrated in a very large number of his figures that the accessory fibre ended in the same sole-plate as the myelinated fibres (and some of these figures were from intercostal muscles), one can surely definitely state that some muscle-fibres at least are innervated by both systems. Histologically it would be extremely difficult to show the double innervation, somatic and sympathetic, on every muscle-fibre, but some individual fibres are certainly proved, in my reading of Boeke's work, to be doubly innervated.

Of Agduhr's work, Hunter gave a short account and criticized it on the ground that, as Agduhr stated, his "accessory" plates approached in form to those of the motor-plate, and were by Hunter thought to be non-myelinated collateral branches of myelinated fibres which had not yet degenerated. The particular case he cited was found after five days' degeneration. This, however, is only one particular case, and after a period of ten days similar appearances were found which ruled out the possibility of a somatic fibre on account of its evenness of staining and completeness. Agduhr stated in reference to his fig. 2: "An intact sympathetic nerve with a simple loop formation terminates within the region of the motor-plate. There are thus instances of sympathetic nerve-fibres in the musculature of the extremity that terminate within the region of a motor-plate." Clearly this means a double innervation of these fibres at least, leaving out of account if necessary the larger accessory plates whose sympathetic nature Hunter questions, although Agduhr remarked "It is as a rule easy to distinguish, even in preparations where all the nerves are intact, between motor and sympathetic terminal plates of nerves."

The histological work that Hunter brings forward to prove his contention that the sympathetic and somatic fibres do not end on the same muscle-fibre has not yet been published, and only a short note of it is given in his lectures. Hunter and Latham examined the mode of ending of the nerves in the limb muscles of the goat and fowl, which were used by Hunter and Royle in their experimental work. "In no cases were they able to find a muscle-fibre receiving both kinds of nerves." Latham, however, distinguished hypolemmal sympathetic

nerve on the *slender* muscle-fibres. As Hunter and Royle do not state that they found any variation in size in the normal muscle in the goat, and state definitely that very little variation could be seen in the normal muscle of the fowl, it is doubtful to what Latham refers when he speaks of *slender* muscle-fibres.

(4) *On Neuro-muscular Spindles.*

Of the older descriptions of the neuro-muscular spindles no mention will be made here. At that time these organs were considered to be germinating centres for muscle-fibres, and very little was known of the nerve-fibres connected with them. It was only when fuller descriptions were given of their nerve terminations that their sensory function became evident.

Sherrington (1894) [55] before describing his own observations gave a review which may be consulted for the older work. In experiments after section of the motor nerve-roots (anterior) he always found that every spindle seen still possessed perfectly sound myelinated nerve-fibres. He, therefore, proved them to be sensory organs. From his own observations in cats and monkeys he gave the following account: The lamellated capsule completely enclosed the periaxial lymph space through which the muscle-fibres of the spindle ran. At the proximal polar region these primitive muscle-fibres, two to twelve in number, were of the "red" (Ranvier) or "trübe" (Grützner) variety; as they penetrate into the organ, they split longitudinally into two or three daughter fibres. There they showed numerous nuclei in the thickness of the fibre, and often the marginal sheet of the substance of the fibre was alone striated. In the equatorial region the surface of the fibre was encrusted with a sheath of nuclei. At the distal polar region the muscle-fibres resembled in appearance those of the proximal polar region.

The nerve-fibres of the posterior root passing to the spindle were large myelinated fibres, 7 to 17 μ in diameter. They showed a very well marked sheath of Henle. Before they penetrated the capsule the internodal segments were from 600 to 900 μ long, while inside the spindle this distance was shortened immediately to 80 to 130 μ. Inside the sheath the fibres usually divided and became less thickly myelinated, although their diameter remained the same or slightly increased. The nerve-fibres showed a serpentine course and ended in wide, flattened expansions, which Sherrington took to be the annulo-spiral ending of Ruffini.

It is most interesting that Sherrington, with the gold chloride method, could not satisfy himself of the existence of motor end-plates. But after removing a piece of the sciatic nerve, preventing regeneration and waiting 150 days, he found all the ordinary muscle-fibres of the gastrocnemius degenerated, while the intrafusal muscle-fibres were quite normal. To quote his conclusion: "The intrafusal muscle-fibres seem in regard to their nutrition to be largely independent both of the afferent and of the efferent nerves of the muscles, if one may judge by absence of obvious degeneration in them five months after total denervation."

Sherrington did not observe any of the smaller afferent nerve-fibres entering a muscle-spindle. He did not find any spindles in the intrinsic eye-muscles nor in the intrinsic muscles of the tongue.

Ruffini (1898) [52] gave a very minute account of the structure of the muscle-spindles of mammals, with special reference to the cat. The description of the intrafusal muscle-fibres and their endings alone need be considered here. He described the muscle-fibres as showing very well marked striation and nuclei more abundant than in the ordinary fibres. The nerve-endings in the spindles he divided into three types: the primary ending was formed from a very large medullated fibre which divided into two or three non-myelinated branches, and these flattened and wound themselves round the muscle-fibre in the form of rings or spirals, the annular or spiral endings, or a mixed form, the annulo-spiral. The second ending was formed from medullated fibres, never so large as those of the primary ending, and were found on either side of the annular or spiral ending. The nerve-fibres to this ending pass in with the primary fibre, but often enter the spindle from another nerve branch. The ending itself he described as having varicosities and suggesting sprays of flowers. His third type of ending, or plate-like termination, is of special interest in view of more recent work. These he stated were very variable in size and form, some being larger than and some smaller than the Rouget plates in neighbouring ordinary muscle-fibres. Ruffini could find no granular sole-plate nor eminence of Doyère. These endings were formed from very delicate nerve-fibres, which he thought to be branches of larger fibres; they could be found entering with the latter to the primary or secondary endings, but sometimes came from a different nerve branch and entered the spindle by themselves. He found no branching of these fine fibres inside the spindle, so that each ending had a fibre of its own. From a comparison of a large number of spindles, Ruffini stated that the primary

and plate-like endings are constantly present. In summing up he concluded that there were no motor endings on the spindle muscle-fibres, as on analysis of the plate-like endings he thought them sensory. He never found a fibre from a motor-nerve bundle passing to the spindle.

Golgi (1903) [26] described the muscle-fibres of the spindle to be distinguishable from the ordinary muscle-fibres by three points: (1) they were thinner, (2) constantly furnished with much more abundant nuclei of the sarcolemma, (3) throughout their whole length many of the nuclei lay inside the muscle-fibre and had round them granular protoplasm. They were described by him as being like embryonic ordinary fibres.

Perroncito [46] described fibres passing to the muscle-spindle in lizards which could hardly be other than motor. He was of the opinion that the muscle-spindle had motor as well as sensory nerve connections. In his later paper [47], he found very fine non-myelinated fibres passing into the muscle-spindles, as in this situation they were easily demonstrated. His figures show a very complex network of these fibres both in the capsule and inside it. The ultimate connections in this organ he could not determine but thought that in some cases they were in contact with the muscle-fibres. These thin non-myelinated fibres entered the spindle in the Henle sheath of the medullated fibre, and not with the blood-vessels.

Golgi (1919) [27] was also of opinion that the muscle-fibres in the spindles had both sensory and motor terminations upon them.

Dogiel (1902) [22] described the nerve-endings of the muscle-spindles. He found one or more thick medullated fibres passing into the capsule and ending in non-myelinated branches round the spindle muscle-fibres as Ruffini described. In addition to these, two or three thin medullated fibres formed endings, either inside or outside the capsule, which were of various forms, but were all small and plate-like. These he considered to be motor in function. He also found passing in along the blood-vessels sympathetic nerve-fibres, as Huber and De Witt [32] described. They evidently were connected only with the blood-vessels.

Cilimbaris (1910) [20] made investigations on the muscle-spindles of the extrinsic eye-muscles of various animals. He found them present in these muscles in the sheep, roe, stag, goat, cow and wild boar, but absent in the horse, pig, dog, cat, fox, rabbit, hare and rat. The spindle muscle-fibres were found to be often small but were sometimes large,

and both sarcoplasm-rich and sarcoplasm-poor fibres were seen in the spindles. Inside the capsules of the spindle the muscle-fibres divided dichotomously and these smaller daughter-fibres united together at points to form a network. At the site of the sensory nerve-ending he described globules (Bläschen) inside the muscle-fibre. These were only found in this situation and were related to setting up of afferent impulses in the sensory endings. The nuclei of the spindle muscle-fibres were often placed more centrally than in ordinary skeletal fibres, but the contractile substance was the same as in ordinary fibres.

Of the nerve-fibres passing to the spindles the majority were medullated. He believed that in isolated cases he had seen non-myelinated fibres passing to the spindles but could not be definite on this point, and in these few cases he thought them vasomotor fibres. While he held that both motor and sensory fibres passed to the spindles, he could not agree with those who said that the thick medullated fibres were sensory and the thin medullated fibres motor. He found the calibre of the fibres subject to great variation; typical motor end-plates were sometimes found formed by a thick medullated fibre and sometimes by a thin fibre. In the same way the sensory ending could be formed from either large or small medullated fibres. He was convinced that there was no difference in the motor supply of ordinary muscle-fibres and the spindle muscle-fibres. In further proof of this he cited cases like those of Perroncito, where a motor-fibre divided into two branches, one of which ended inside the spindle on a spindle muscle-fibre, while the other ended on an ordinary muscle-fibre. Also he described a motor-fibre inside the spindle dividing into two branches, one of which ended on an intrafusal muscle-fibre and the other, after passing out, on an ordinary muscle-fibre. He never found more end-plates in the spindle than there were muscle-fibres, and no case of one muscle-fibre with two motor-plates was seen. These motor end-plates, he stated, in no way varied from the motor end-plates on the ordinary muscle-fibres. He noted the presence of the ultra-terminal fibres of Ruffini in a number of his end-plates on the spindle muscle-fibres, and they often passed outside the spindle to end on the ordinary muscle-fibre.

The sensory endings described by Cilimbaris resembled those seen by others, only differing in the "Bläschen" formations being present in the muscle-fibres where the sensory endings were situated He pointed out that while the spindle muscle-fibres had both sensory and motor terminations upon them, there was always a termination-free part of the muscle-fibre between the two.

Sutton (1915) [56] found muscle-spindles in the extrinsic eye-muscles of embryo pigs, while Cilimbaris could not find them in those muscles in the adult domestic pig, although he did see them in the wild boar. In the earlier stages a very complicated network of fibres was found in the muscle, but as the embryo developed the plexus formation became less and less, until large branching fibres were left and these became myelinated. He found the early spindle muscle-fibres at first to be striated throughout their whole length, but later this striation was lost in the intracapsular part. It is also interesting that he described the capsule as a late development.

Kulchitsky (1924) [35] described the muscle-spindles in python muscle and divided them into a simple form and a more complex one, the small and large spindles. He maintained that the spindle muscle-fibres retained their cross striation throughout their whole length, and did not show any change in thickness inside the capsule. Usually one medullated fibre was found entering the capsule, and after losing its myelin formed ribbon-like or spiral rings embracing the muscle-fibre. The endings he thought were on the surface of the fibre and were sensory. Besides the myelinated nerve-fibres Kulchitsky found non-myelinated fibres which he thought were sympathetic, and which ended in "terminaisons-en-grappes" on the muscle-fibre of the spindle. These he found outside the limit of the capsule and several endings could be found on one spindle muscle-fibre, but he also described non-myelinated fibres passing inside the capsule to end on the muscle-fibres; these, however, he did not show in his figs. 10 and 11 to end in "terminaisons-en-grappes," although he believed they did end in this way. These non-myelinated fibres he considered to be quite separate from the myelinated fibres, which he described in the rest of the muscle, and to be motor in function.

In his later paper [36] on the innervation of frog's muscle he made no reference to muscle-spindles.

Dart (1924) [21], from his observations on Kulchitsky's specimens, made several statements which cannot be correlated with Kulchitsky's own description. In the short oval capsulated spindle the medullated fibre is said to divide into non-myelinated branches and end in plate-like forms within the capsule, while the sympathetic fibres end on the muscle-fibres of the spindle in what he describes as motor sympathetic endings, contrasting them with the sympathetic sensory or "en-grappes" endings.

The resistance to atrophy described by Sherrington he thought

might be accounted for by (*a*) the preservation of primitive characters of the muscle-fibres, and (*b*) the very rich sympathetic motor innervation. Dart also remarked that he awaited confirmation of coarsely myelinated motor-fibres going to a spindle, as Perroncito described.

Part III.—Original Work.

(1) *On the Striated Muscle of the Hedgehog.*

Material.—The fully-grown hedgehogs were killed with chloroform and the muscles dissected out as quickly as possible. When the panniculus carnosus was dissected out it could be seen to receive branches from each spinal segment. These branches run across the sheet of muscle on its ventral aspect and give off as they pass out small branches which pass into the muscle. In the substance of the muscle the small nerve bundles always keep a course at right angles to the length of the muscle-fibres. All the observations were made on this muscle. Small pieces of the muscle were quickly removed and carried through by the method now to be described.

Method.—This was the Fischer modification of Ranvier's method as used in Golgi's laboratory, and will be given in detail.

(1) Immerse small pieces of tissue in a 25 per cent. solution of pure formic acid, and, depending on their size, leave for ten to fifteen minutes. See that the immersion is complete. During this period tease the preparation a little to get better penetration. Too much fluid should not be used.

(2) Take the pieces quickly from the acid solution and place on a *clean* folded duster, cover with another fold, and press gently to absorb as much acid as possible.

(3) Pass to a 1 per cent. solution of gold chloride, just sufficient to cover the pieces completely, and shake the pieces in it. No iron instrument must be used in this or subsequent baths. Bone-pointed forceps or metal forceps covered with paraffin wax must be used. It is advisable to cover the dish with a blue or yellow glass. Leave twenty minutes at the most.

(4) Carry out (2) again with clean duster.

(5) Pass tissue into a 25 per cent. solution formic acid. Use just enough to cover the pieces of tissue. Leave in absolute darkness for twenty-four hours.

(6) Proceed as in (2) again.

(7) Pass to pure glycerine and leave in ordinary light in a closed

vessel. The longer the tissue is left in glycerine the clearer does the preparation become. (Some of my best specimens of frog muscle are five years old.)

Cleanliness is paramount in order to get good results; my solutions were made up in double- or treble-distilled water.

The preparations are made by teasing small pieces of the stained muscle or nerve and mounting these in pure glycerine. The permanent preparations are ringed with a cement or gold size.

The method of final preparation, that of teasing, has very definite limitations. The complete continuity of the fine nerve-fibres and fibrils must of necessity be sacrificed in many instances in the interests of clarity. The definite establishment of continuity in even one case is therefore of extreme importance and totally outweighs the fact that it has only been seen once. The teasing then, while it sacrifices the multitude of fine fibrils in the preparation, does in some few and fortunate specimens show their course and continuity with great clearness. This method is therefore only capable of showing continuity throughout a short distance of their course, unless in exceptional cases.

The nerve-fibres when well stained appear intensely purple or black. If, therefore, a thick nerve-fibre is accompanied by a very fine fibre of very much smaller diameter, it is obvious that in two positions out of the large number of possible positions which the thin fibre may occupy on the periphery of the large fibre, will it be clearly seen when viewed from above. At all the other possible positions it will be obscured by the dark thick fibre, and it is extremely difficult on focusing to be sure of its existence against the dark thick fibre as it is itself dark. It is therefore possible for a fine accompanying fibre to pass out of sight, and yet retain its independence of the large fibre, unless it can be traced to pass out of sight at a node of Ranvier, at which point only do myelinated fibres in their course give off myelinated or non-myelinated branches.

(*a*) *The muscle-fibres.*—In order to examine the whole length of a single muscle-fibre, which is extremely difficult in teased preparations of the panniculus carnosus muscle, the small pieces of muscle after being in glycerine for a long period were washed in distilled water and placed in a weak solution of nitric acid to dissociate the different elements. This caused a great shrinkage, but otherwise did not seem to harm the tissue. The single muscle-fibres could then be mounted, a number on one slide, in glycerine.

This method of preparation reveals the fact that the muscle-fibres are peculiar in that they are all long and fusiform, tapering towards both ends very slowly from the middle of the fibres. They are unlike the usual striated fibres which appear as parallel-sided cylinders for nearly their whole length and only present rounded ends just at their attachment to the tendon. A considerable degree of variation in size of the individual fibres was found, some of the smallest fibres having a diameter at their middle of one-half or one-third of the diameter of the larger fibres at the same point. Therefore, where the whole length of a fibre in a teased preparation cannot be followed out it becomes a matter

FIG. 1.

of great difficulty to decide whether the particular fibre is really a small fibre or the tapering end of a large fibre.

With reference to the plurisegmental innervation of each fibre, it is interesting to note here that the muscle-fibres are much longer than is the distance between the segmental nerves as they pass over the whole muscle. Some of the larger fibres, which are also the longest, are long enough to have three segmental nerves passing across them at different points.

The cross-striation in the dissociated fibres is not very well marked; this I think is due to the staining, as in some of the other preparations the cross-striation is well marked. As to the existence of two types of

muscle-fibres the following points may be made. On account of size two types of fibre could not be distinguished clearly, as all sizes between the largest and the smallest could be found. The degree of longitudinal striation is more interesting. Some of the fibres show a much coarser longitudinal striation than do the others, and while intermediate grades may be found the two sets might be more clearly differentiated by this than by size. In addition to the more deeply stained longitudinal striation these fibres show very deeply stained little elongated masses of sarcoplasm, in the centre of which may be seen clear oval structures, the muscle nuclei. These elongated masses may be longer and contain nuclei at equal intervals in their course. These fibres would therefore appear to have a larger amount of sarcoplasm. The number of the nuclei in the longitudinally striated fibres does not appear to be more numerous than in the fibres not showing this marked longitudinal striation. In the latter fibres the nuclei are less clear, as the sarcoplasm round them is not deeply stained. This, it seems to me, raises the question at once as to whether these markedly longitudinally striated fibres are not simply fibres which are more deeply stained. It is necessary to state that in this muscle, for a reason to be given presently, uniform penetration and therefore staining is very difficult.

The cross-striation is in these fibres as a rule very well marked. The size of the deeply stained longitudinally striated fibres varies considerably, and while a number of these are of the smaller sizes, one or two of the larger fibres have also been seen in this condition. The total number of these fibres is very small compared with the number of the fibres not presenting these peculiarities. By no means all the small fibres show them. In view of the appearance seen in frog muscle where two different types of fibres are known to exist, it seems to be impossible to say definitely that there are in the panniculus carnosus two distinct types of fibres, but appearances suggest that for some reason the sarcoplasm in a few of the smaller fibres stains more deeply and may be present in larger amount than in the other fibres.

The arrangement of the muscle-fibres in the sheet of muscle shows that the individual fibres interdigitate with one another, so that at any one line drawn transversely across the muscle one finds all stages, from the very thin ends up to the large diameter of the middle of the fibre. This makes the muscle very difficult to tease without injuring a large number of the elements, and makes uniform penetration of the staining reagents and consequent uniformity of staining very difficult.

(*b*) *The constitution of the nerves entering the muscle.*—Observations

were made of teased nerve bundles as they entered the muscle, or of bundles in the muscle at some distance from their endings. These bundles were stained by the same method. This investigation was made to see if there were any fine non-myelinated fibres present in the intramuscular nerve or nerves as they enter the muscle, and, if so, in what numbers were they present. That is, it was an attempt to eliminate a criticism which might be levelled at the demonstration of non-myelinated fibres near the region of the motor-plates of Rouget, that in this situation these non-myelinated fibres are simply small non-myelinated branches of the myelinated fibres in or near this region. The demonstration, then, of a number of fine non-myelinated fibres in the nerve at its entrance into the muscle would in part eliminate this objection, as it is much more reasonable to suppose that the fine non-myelinated fibrils in the region of the motor plate are the continuations of some, at least, of the fine non-myelinated fibres found in the nerve some distance proximal, than to postulate that they are new branches of the myelinated fibres near the end-plate, and that the non-myelinated fibres found proximally have some other termination before they reach the region of the motor end-plates.

In good preparations the myelinated fibres are deeply stained and their nodes of Ranvier well marked. There is found to be extremely little or no branching of these fibres at the nodes. The great majority of these are large well-myelinated fibres showing some variation in size. Smaller myelinated fibres are also seen in smaller numbers, but easily distinguishable by their nodes from the next type of fibre to be described.

A relatively large number of non-myelinated fibres can be found. These are easily differentiated from the myelinated fibres. They do not have the sharp outlines of the myelinated fibres and show no sign of segmentation at nodes of Ranvier. They are less deeply stained and vary in size from that of the small myelinated fibres to extremely fine fibrils. They show in their course the characteristic nuclei of the pale fibres. Some of these larger pale fibres divide up into a number of thin fibres, which may pass on singly or reunite with their fellows, or unite with other thin pale fibres, showing that the tendency to plexus formation is already present in the nerve. They may be found single, accompanying a thick medullated fibre, or in groups twisting and twining together. They are clearly distinct from the myelinated fibres, and are not found as branches of them.

The same facts could be observed in the smaller intramuscular

nerves some distance from the muscle-fibres they supplied. The existence, then, of a separate system of non-myelinated fibres is definitely proved in these nerve bundles.

(c) *The motor-endings.*—On even a preliminary examination of the motor-endings of the medullated fibres, the variation in size, shape, and form is striking. The form of the motor-plate in this muscle is very complicated and not unlike type I, as described by Kulchitsky in snake muscle. After long examination of many preparations it has been impossible for me to make any division of these varying forms into

FIG. 2.

FIG. 3.

definite classes or types; while some variations resemble in some respects the "terminaisons-en-grappes," it has been impossible to make any distinction between these forms and the more typical Rouget plates, as all forms intermediate between these two are found not in a few cases but in many.

A more detailed description of some of these variations will now be given.

The medullated fibres as they pass across the muscle-fibres to which they are connected show some branching at the nodes of Ranvier. It is of interest that while a medullated fibre may in some cases appear not to divide at all but to end in one Rouget plate, which is usually

large in size, the fibre may as it passes give off three or four short branches, all of which end in large plates, and then end itself in a large plate. What relation this has to the numerical method now in use of counting the fibres on cross sections of a nerve in determining the functional activity of that nerve, is not quite clear. But if one nerve-fibre may either innervate one or five muscle-fibres, as it appears, this fact must be taken into account.

Near the point of entrance of the medullated fibre into the muscle-fibre the myelinated sheath may be lost. In a number of cases this may occur at some distance from the plate. The branches of the medullated fibre which form end-plates may also be non-myelinated, or at least very thinly myelinated, so that some motor end-plates may be found which have a medullated fibre while others have a non-medullated fibre. But this distinction seems to be of very little value,

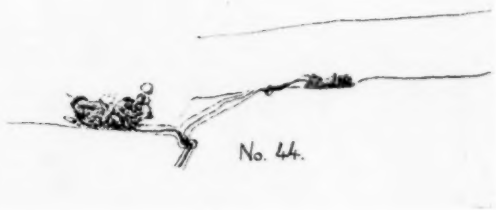


FIG. 4.

as these non-myelinated fibres are simply branches of the axon of the medullated fibre, and must have exactly the same origin and function. In some cases where the further course of one of these non-myelinated fibres is obscured it seems to me unnecessary to suppose that it is a non-myelinated fibre throughout its course, when this form of branching —non-myelinated fibre from myelinated—is so common in all the preparations.

Some of the branches are definitely medullated, though by no means so heavily as the parent fibre. While it is true that in some cases this apparent loss of myelin proximal to the end-plate may be due to stretching or to the teasing of the preparation, in other cases it can be definitely stated not to be due to this mechanical strain.

Examining now the mode of entrance of the fibre into the muscle-fibre, in many cases, especially in those plates showing an oval or rounded form, the nerve-fibres pass directly under the sarcolemma

without dividing. In others the fibre may divide into two or more branches, each of which enters separately into the muscle-fibre. This is often seen in the case of two branches, and a special form of end-plate to be described later is often associated with it. Some of these branches are collaterals and will also be described later in their terminations.

A peculiar form of this branching has been observed in some of the specimens. As the two branches pass together to the plate, separated only by a small angle, the sheath of Henle appears to be greatly thickened and corrugated and contains a large number of nuclei. Through this the axon cylinders pass in a spiral fashion. One of this form may be seen in fig. 13, which, however, is complicated by the further branching of the fibres to supply other plates. It can, however, be seen in many cases where branches supplying one end-plate only are present.

Variations in size of these motor end-plates are marked, some of the endings only occupying approximately one-quarter of the area of the largest plates seen. The largest plates lie as a rule in the middle portion of the largest fibres, that is, near their points of maximum diameter. They are formed more commonly from nerve-fibres which are medullated up to, or very close to, their point of entrance into the fibre, and much less commonly from fibres which lose their myelin proximal to their entrance into the muscle-fibre. The smaller end-plates are more commonly formed from non-myelinated branches or from thinner myelinated fibres, but in some cases a quite thick myelinated fibre may form a smaller plate. These smaller plates are often found on muscle-fibres of smaller diameter, which are frequently really the tapering ends of a large muscle-fibre. Quite often, however, these small plates are seen on the larger muscle-fibres where their diameter is still relatively great.

Some conclusion as to this great variation in size of the motor end-plates may be drawn from an examination of the dissociated muscle-fibres described above. This was primarily undertaken in order to be able to follow out easily the whole length of a single muscle-fibre and to see if more than one ending could be found on it in view of Agduhr's statement that the individual fibre is innervated plurisegmentally. Agduhr's specimens from limb muscles show the different segmental plates very close to one another on the muscle-fibre. In a muscle such as the panniculus carnosus, no joining together of the spinal roots occurs, so that one could not expect to find end-plates close together on the

single fibres. In favourable cases two or more end-plates separated by a long distance have been found on single fibres (fig. 1). Now as very few fibres of the nerve bundles show a longitudinal course, unless for a very short distance just proximal to their ending, and the distance between the end-plates is approximately the distance between the segmental nerves, I think it can be safely concluded that in these cases single muscle-fibres are innervated plurisegmentally. Numerous instances were not found, but this was doubtless due to the difficulty of keeping the long single fibre intact in the process of dissociation and mounting, and to the fact that while one end of the muscle-fibre might be appropriately stained to show an end-plate, the other end was often too deeply or too lightly stained.

It is found that the larger motor end-plates are near the middle of the fibres, while smaller plates are often seen nearer the ends of the fibres. That both the end-plates on the one fibre are motor is proved by their hypolemmal position and granular sole-plates. The plurisegmental motor innervation of the single muscle-fibre can therefore be confirmed for at least some of the muscle-fibres of this muscle. It differs only from Agduhr's demonstration in that the plates are very far apart on the single fibre.

During these observations it was easy to examine the endings on the more longitudinally striated muscle-fibres. I was not successful in finding such a fibre with a plurisegmental innervation, not, I think, because they do not exist, but on account of the very small number of these fibres which could be found and followed for any considerable distance. That these fibres with well-marked striation are innervated by exactly the same type of nerve-fibre as the other muscle-fibres, and with the same type of end-plate, could be perfectly definitely established. These fibres received a myelinated fibre, often a very thick one, which is contrary to the idea that they might have only a non-myelinated sympathetic nerve supply.

It is to be regretted that these dissociated preparations do not show the very fine non-myelinated fibres to be described later. This is no doubt due to the method of preparation, as it is quite unlikely that such fine fibrils would withstand the treatment.

Great variations in the form of the Rouget end-plates are found. In the hedgehog the terminal ramifications of the axis-cylinder have a very much more complex formation than is seen in many of the other vertebrates—much more complex in my preparations than those seen in lizard, rat, rabbit or human muscle. The branch or branches of the

myelinated fibre, after passing through the sarcolemma, divide up into fine branches. These show in many specimens a great deal of anastomosis, so that an end-net is formed. Parts of these branches, either the terminal points or the points of junction or anastomosis, present thickenings which are very deeply stained. The terminal thickenings are often rounded or knob-like. The degree of branching and anastomosis varies very considerably. In some cases one part of this terminal arborization is very much more marked and gives the appearance of a central whorl, or wheel with radiating spokes, set in the less well marked branching of the remainder of the terminal ramifications.

In some cases where two branches of nearly equal thickness pass into the end-plate they each form terminal ramifications which remain discrete in the same sole-plate, suggesting the appearance of a double plate. In other cases, where the two branches are of unequal thickness, the large branch passes in and forms the large part of the plate, while the fine fibre passes often to the most distal point in the terminal ramifications. It is curious to notice this long course of the thin branch to reach this point furthest from its starting point.

The shape of the area occupied by the terminal ramifications in the plate is frequently rounded or oval, but many shapes are seen. Elongated forms are fairly common, and less rarely quite irregular forms can be observed. The smaller Rouget plates show similar variations in shape, but much less markedly than the larger plates, as the former are much more commonly rounded or oval.

In all preparations which were properly stained a granular sole-plate could be seen extending over a slightly larger area than the terminal ramifications. In some cases it was much more darkly stained than in others, but it was invariably present. At the edge of the granular sole, in a number of cases, the nuclei of the sole could be seen as large clear areas.

As has been mentioned above, no difference could be found in these motor-plates on the muscle-fibres which were markedly longitudinally striated. All that may be said is that the rounded or oval form was seen on them more commonly than the more irregular forms, and the sole-plate was usually very well marked.

From the foregoing account, it can be seen that it is impossible to attempt to divide the motor end-plates into two types. Real "terminaisons-en-grappes" have not been found, and although some forms approximate to them, all transitional stages between these and the

typical round or oval Rouget end-plate are numerous, and so classification becomes impossible.

Where a myelinated fibre branches before its entrance into the muscle-fibre the small branch may be non-myelinated, and instead of passing into the end ramifications of the plate, as already described, it may form a small discrete end ramification on the same muscle-fibre, either in the same granular sole or in a small collection of granular substance near the main ending. This is the collateral type of fibre. A number of cases like this have been found. They must be clearly distinguished from the accessory fibres presently to be described. The collateral is simply a branch of the myelinated fibre near its ending, and

FIG. 5.

FIG. 6.

appears to me to be simply a slight irregularity from the usual type of branching where all the branches end together on the same sole-plate.

A more interesting type of fibre is that seen in fig. 6, which I take to be an ultra-terminal fibre. It arises in the terminal ramifications and passes round the muscle-fibre to a completely different level from the end-plate. It is of course impossible to show this in the diagram. In this course upwards to the right and then to the left it has upon it two clear nuclei. It ends in a small ramification, the exact position of which it is extremely difficult to determine. It may be situated either on the opposite side of the muscle-fibre from the Rouget plate, or on a different muscle-fibre lying above.

Another extremely interesting fine non-myelinated fibre is that seen in fig. 7. It is impossible to determine whether it is accessory or somatic, that is a branch of a myelinated fibre, as its continuity is lost just previous to the myelinated fibre, and its further course, as distinct from that fibre, or as a branch of it, is hidden. The medullated fibre passes upwards to end in a plate which is obscured by very deep staining, while the fine non-myelinated fibre passes across a muscle-fibre to lie, it appears, between two muscle-fibres. It divides into three branches; one passes upwards with slight varicosities and ends after a short course, while the other two, each of which has varicosities, and one nucleus upon

FIG. 7.

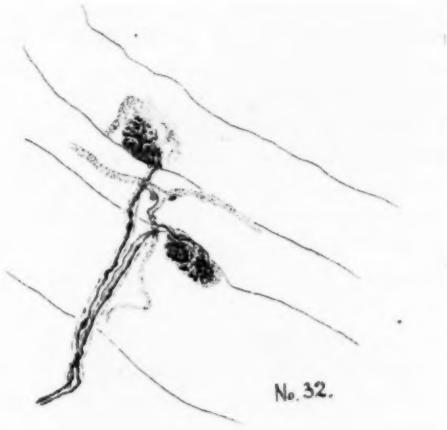


FIG. 8.

it, appear to join together again and end in a long loop. The whole termination appears to be outside the muscle-fibre, but whether in connective tissue or not it is difficult to state. It may represent one of Kulchitsky's free terminations in the connective tissue of muscle, but of this I am by no means certain.

The accessory fibres.—The presence of these fine non-myelinated fibres has already been described in the small nerve branches entering the muscle. A system of fine non-myelinated fibres can be found in the well-stained preparations in the region of the Rouget plates in teased specimens of the muscle. In a large number of preparations they were not found, as the staining needs to be extremely good to show them on account of their very delicate structure. I have no doubt that they are

the continuations of the fine non-myelinated fibres already described in the nerve bundles. They will now be referred to as the accessory fibres, as they appear to be identical with those described by Boeke.

The accessory fibres are found, as a rule, accompanying the medullated fibres in their course to their Rouget plates. The exact position of these fibres, whether inside or outside the sheath of Henle, is difficult to determine. At certain points they appear definitely outside this sheath, but in a large number of instances they appear to be inside it. The latter appearance is in many cases due to the fact that being very many times smaller in diameter than the medullated fibre, and being viewed only from above, these fibres will, unless they be at the extreme right or left edge of the sheath, appear inside the sheath instead of below or above it. At some point in their course they often take up this extreme lateral position and appear to be definitely outside the sheath. In other cases they do not.

They are usually single where found accompanying one medullated fibre, but in some cases more than one can be found in this situation. At intervals along their course they have elongated nuclei, which are sometimes clear and highly refractile, and sometimes more deeply stained. At some points they have a tendency to break up into two or three finer branches, only to reunite into the single fibre after a very short distance. This peculiarity is of interest as Boeke figures it in many of his drawings.

Near the end-plate the accessory fibres present various arrangements according to which they can be divided into four different types. These types are different only in this respect, and cannot be differentiated by any peculiarity of size or structure.

Firstly, the accessory fibres may pass with the medullated fibre into the same sole-plate and appear to end there (fig. 8). Their exact point and type of termination in this situation cannot be determined in my preparations. They become completely obscured by the very deeply staining ramifications of the myelinated fibre with its knob-like end-points and by the granular sole-plate. It can, however, be stated after thorough examination that in these cases they do not pass out from the region of the sole-plate of the Rouget ending. This is not due to the further course of the fibre being interrupted by the teasing, as they can be definitely seen to enter the granular sole-plate. Whether they end, as Perroncito described in the lizard, in a complicated end-net with branches into the granular substance, or terminate by joining the ramifications of the medullated fibre as Gemelli observed, or end in

entirely separate small end-nets in the heart of these ramifications as Boeke described, it is impossible to decide in these preparations. It is unfortunate that their exact termination cannot be seen, but it is only

FIG. 9.

FIG. 10.

in those cases where the myelinated fibre, its end ramifications and the granular substance are all very deeply stained that the existence and course of the accessory fibres can be followed out at all, and this, of

course, obscures their final termination in this first type. Fortunately, however, they have other final endings which can be clearly seen and which reveal their nature more conclusively.

Secondly, the accessory fibre may pass away from the medullated fibre just proximal to the latter's formation of the Rouget plate, or pass over or along the side of the Rouget plate to end after a shorter or longer course in an isolated small plate-like ending on the same or on a neighbouring muscle-fibre (e.g., fig. 10). In this class the termination of the fibre in a distinctly separate end-apparatus is perfectly clear. Its structure is simply that of the Rouget plate in miniature, with the formation of knob-like expansions in a bed of granular nucleated sole substance. In some cases the heavily-stained knob-like appearance is not evident and a simpler loop-like structure is seen. A large number of instances of this type of termination has not been found in which the identity of the accessory fibre could be followed out for any distance. In a large number of cases the independence of the accessory fibre cannot be shown definitely. It is, therefore, possible to look upon this larger number of cases as simply collateral fibres of the medullated fibres, and not as accessory fibres. That undoubted collateral fibres do exist has already been mentioned, but a number of these doubtful instances seem to me to be more probably accessory fibres than collateral, but this cannot be proved. The very small diameter of these accessory fibres makes it possible for them to run for long distances just under or above the thick medullated fibres, so that their independence is not obvious, and the appearance suggests that they are branches of the myelinated fibres. As stated above, however, some of the accessory fibres can be traced to their endings over a long course and they are certainly not collateral fibres.

Thirdly, the accessory fibre associated with the myelinated fibre just before its termination may pass from the region of the Rouget plate, enter into intimate connection with a neighbouring capillary and run along in contact with its wall (fig. 14). The number of instances in which this has been seen and followed for some considerable distance leads to the inevitable conclusion that this is not a chance connection, or a method by which the accessory fibre passes to another muscle-fibre or other destination, but that these accessory fibres do in fact supply the capillary wall in the region of the Rouget end-plates.

When a small arteriole is examined and the thicker non-myelinated nerve-fibre running along its wall is followed to the capillaries which branch out from it, these undoubted sympathetic fibres are seen

to occupy exactly the same relations to the capillary, as regards intimacy, nuclei along their course and thickness, as do the accessory fibres of this type. This observation has been repeatedly made, and

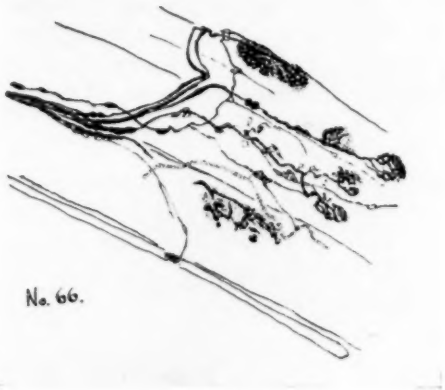


FIG. 11.

FIG. 12.

seems of the greatest importance in interpreting the significance of the accessory fibres. It also demonstrates the probability of the capillaries in muscle being supplied by fibres which reach them by two different routes.

One special case seems of still greater importance, that shown in fig. 9, in which an accessory fibre is seen ending in profile on a muscle-fibre, after a short course from a leash of medullated and accessory fibres. The accessory fibre divides up into branches, most of which end in darkly staining end-knobs forming the small plate on the muscle-fibre, while one of these branches pursues a downward course and becomes intimately associated and connected with a capillary. This demonstrates conclusively that the accessory fibres which supply the capillaries and those which have small end-plates are of exactly the same origin.

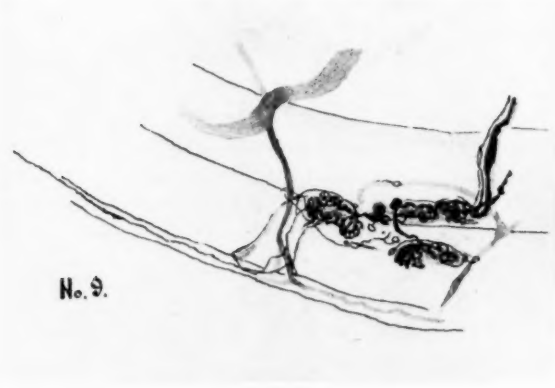


FIG. 13.

Fourthly, the accessory fibres may pass from the myelinated fibre in the region of the Rouget plate, or from a small nerve bundle directly, to form a plexus by anastomosing with other accessory fibres, from which branches may pass off to have endings of the second or third types. These plexuses are easily demonstrated lying between the muscle-fibres in the substance of the muscle.

No ganglion cells have been found in relation to this non-myelinated plexus.

(*d*) *The neuro-muscular spindles.*—A large number of these organs were examined. In this muscle no very simple spindles were found, and the majority contained from two to five muscle-fibres. The spindle muscle-fibres were small in diameter and tapered out on either side of the equatorial region for a long distance. In the gold chloride specimen it has been impossible for me to see the division into daughter-fibres inside

the capsule, but it is certain that the number of muscle-fibres inside the capsule is larger than at either pole outside the capsule. These spindle muscle-fibres have as a rule a coarsely-marked longitudinal striation and little collections of deeply stained sarcoplasm round the muscle nuclei. In some few cases, however, the intrafusal muscle-fibres have no marked longitudinal striation.

The capsule is well shown in these preparations, but does not merit further description here.

The nerve connections of the spindles are of more interest. The endings in the equatorial region are the typical annulo-spiral and flowery terminations described so fully by Ruffini. The first of these is seen to be more extensive and constant than the second. It is formed from a very thick medullated nerve-fibre, which often enters the capsule near the equatorial line; of all the intramuscular nerve-fibres it is easily the largest medullated fibre to be seen. While there is often one of these thick fibres, sometimes there are more than one.

The plate-like endings on these muscle-fibres are found as a rule outside the capsule towards either extremity of the fibres. In all the spindles which I have examined these endings are formed from medullated fibres. The nerve-fibres are not so thick as those forming the annulo-spiral ending, but in every case they are definitely medullated fibres, of about the same calibre as those forming the usual Rouget plates. They often enter the spindle with the very thick medullated fibre and travel outside the equatorial region to form their endings. In other cases they are seen to pass to the spindle from a small leash of motor nerve-fibres which supplies the neighbouring ordinary muscle-fibres. In one case, seen in fig. 15, a medullated fibre which passes in from this latter direction is thicker than is usual for this type of fibre.

The endings are like the small Rouget end-plates seen on the ordinary muscle-fibres. They have, I think, a granular sole-plate, but it is difficult on account of the coarsely marked longitudinal striation and the little deeply stained masses of sarcoplasm to be absolutely certain of this. They appear to lie hypolemmally. The form is often oval or somewhat elongated, while in other cases it is round. In their course along the spindle muscle-fibres, these myelinated nerves give off branches which form the end-plates, and it can be quite easily seen, in some cases, that one nerve-fibre ends in two places on the same muscle-fibre. In fig. 16 the medullated nerve is seen to give off a small branch, which immediately divides into two, and these form two plates on the

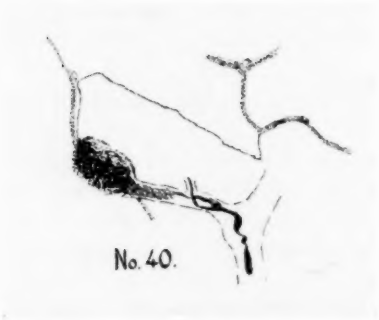


FIG. 14.

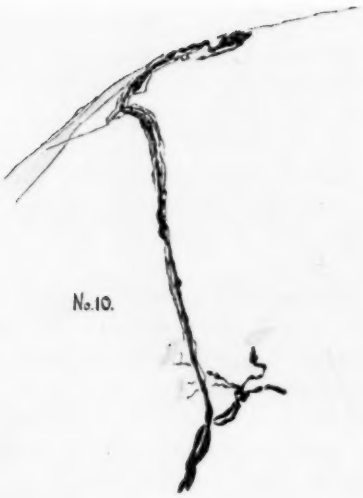


FIG. 15.

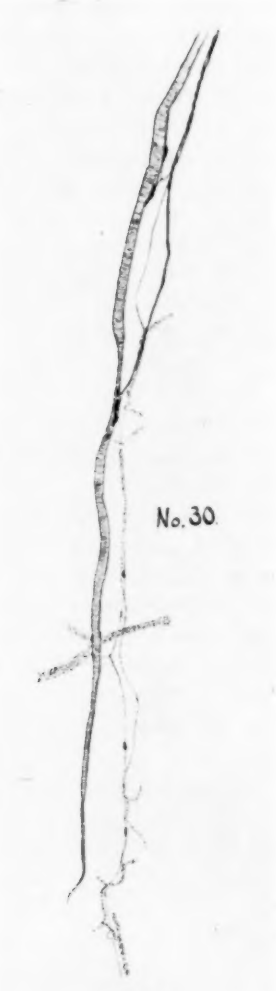


FIG. 16.

muscle-fibre, and the nerve-fibre passing down terminates in a third plate all on the same muscle-fibre.

A number of the accessory fibres have also been seen passing into the spindle, but the exact mode of termination of these very fine non-myelinated fibres cannot be seen in my specimens. Some of the accessory fibres pass in with the thick myelinated nerve and form a very complex network of ramifications inside the capsule, but whether these actually have endings on the spindle muscle-fibres or not cannot be determined. Others of the accessory fibres enter with the nerve-fibres to the plates of the spindle muscle-fibres, and pass with them in a polar direction to end where continuity is maintained in relation to capillaries. Fig. 16 shows a case of this type, while fig. 15 shows a medullated

No. 1.

FIG. 17.

fibre from a motor nerve branch, accompanied by a single accessory fibre which divides up into a number of branches which have unfortunately been broken.

The following short notes have been made of work done by the same method on the striated muscle of different vertebrates in an attempt to correlate and verify some of the statements which have been made in relation to the main work on hedgehog muscle.

(2) *Note on the Nerve-endings in Striated Muscle of the Frog.*

The two types of muscle-fibre in the frog are fairly easily distinguished by size. In my gold chloride specimens, however, they show relatively little difference in staining, the longitudinal striation being only very slightly more marked in the thin fibres. On the basis of this structural characteristic alone, in my preparations it would be almost impossible to distinguish the two types.

Only two points in relation to their innervation will be dealt with. The innervation of the thin fibres is of great importance in relation to Hunter's work. A very large number of these thin fibres can be found to have endings of the Kühne type formed from branches of medullated nerves. To be perfectly certain of this somatic innervation I searched for examples, of which fig. 17 is one, in which a medullated nerve-fibre divides and supplies both a thick muscle-fibre and an adjacent thin muscle-fibre; that is the two types of muscle-fibres that are innervated from the same nerve-fibre. Numerous cases of this can be found. No difference then exists in frog muscle in the innervation of the thin and thick muscle-fibres, for at least a large number of the thin fibres. The other point of note in this muscle is the very extensive non-myelinated plexus of nerve-fibres which can be seen in it in well-stained specimens. Some branches of this plexus are connected with the walls of the capillaries. But I am convinced that the whole plexus is not related to blood-vessels alone, although I have as yet been unable to follow out the branches of the plexus to definite endings in the muscle-fibres or in the endomysium. Some of these thin non-myelinated fibres have a position similar to the accessory fibres, and are seen running with the myelinated fibre outside the sheath of Henle.

(3) *Note on the Nerve-endings in Striated Muscle of the Lizard.*

The thin and thick muscle-fibres in this muscle show, in my few preparations, very little difference in their staining. The thin muscle-fibre, which has an annulo-spiral ending upon it, has a very well marked cross-striation but shows no more marked longitudinal striation than the large fibres.

Accompanying the medullated fibres to the Rouget end-plates very fine non-myelinated accessory fibres have been found. These are definitely outside the sheath of Henle at certain points. While their full course, especially in relation to the medullated nerve near and at the Rouget end-plate, cannot be followed in my specimens, at other points these accessory fibres can be seen to have connections with the fine non-myelinated fibres on the capillary walls.

The thin muscle-fibre mentioned above forms in itself a simple spindle. This fibre lies free in the muscle and is not enclosed in any lamellated capsule. A large medullated nerve-fibre forms a very well developed annulo-spiral ending upon it.

(4) *Note on the Nerve-endings in the Extrinsic Eye-muscles of the Rabbit.*

The fibres of these muscles show considerable variations in size and in the degree of longitudinal striation when stained by the gold chloride method, but cannot be classed into two definite types.

The motor end-plates formed from myelinated nerves are found mainly in the posterior part of the muscle, and the sensory terminations mainly in its anterior part, although they exist to a certain extent in the part supplied with motor end-plates. The Rouget end-plates are found both on the thick and the thin muscle-fibres, and are formed from nerve-fibres which retain their myelin right up to the sarcolemma. They show a characteristic branching outside the muscle-fibres into as many as five or six short medullated branches, which all assist in the formation of the extensive terminal ramifications in a well-marked granular sole-plate.

The sensory fibres give off many fine non-myelinated fibres at the nodes of Ranvier and end by running for very long distances as non-myelinated fibres. These non-myelinated fibres end in small collections of darkly-stained knobs connected together by very fine branches. These may become more extensive and many may be found on one fibre. They show no sign of a granular sole-plate.

I have been unable to find accessory fibres running with the motor fibres, and on account of the large number of non-myelinated fibres which are branches of the sensory medullated fibres, the nature of thin non-myelinated fibres which have no definite connections in their short visible course is extremely difficult to determine in this muscle.

(5) *Note on the Nerve-endings in Human Pectoral Muscle.*

I have to thank Dr. J. Scoular Buchanan for the opportunity of obtaining small pieces of a pectoral muscle in a perfectly fresh condition from the operating theatre.

In this muscle a great uniformity in the size of the muscle-fibres is found, and very little difference between individual fibres can be observed by my method of staining.

The nerve-fibres to the motor end-plates are thinner than those in the hedgehog, and show in a very marked degree loss of their myelin while still at some distance from their termination. This at once makes the question of non-myelinated fibres, which are of other nature than these de-myelinated somatic fibres, much more difficult than in the

hedgehog, as non-myelinated fibres may either be fibres which are non-myelinated throughout their whole course, or simply fibres which have lost their myelin. The Rouget end-plate seen in this muscle is extremely simple in form, as the terminal ramifications are short and thick and do not branch much. In spite of the difficulty of non-myelinated fibres, I have, I think, seen in this muscle extremely fine accessory fibres accompanying a medullated nerve-fibre. Their endings I have been unable to find as yet.

One point is of interest in relation to the muscle-spindles, which are very complex. A very large number of medullated nerve-fibres is found entering the capsule, the largest of which form the annulo-spiral ending and the smaller, passing out to the extremities of the spindle, form little end-plates on the spindle muscle-fibres. The fibres forming the end-plates are definitely myelinated.

IV.—Discussion.

The question of the plurisegmental motor innervation of the individual muscle-fibres does not require any furthur discussion. The existence of such a condition in the panniculus carnosus of the hedgehog has already been described, and the points in which it differs from the demonstration given by Agduhr for limb muscles have been noted. What physiological significance can be placed upon it, it is difficult as yet to suggest. It may, however, like the sympathetic innervation, be related to the tonic activities of the striated muscle. For example, it may in some way have to do with the inhibition of tone in reciprocal innervation.

The existence of two types of muscle-fibre throughout vertebrate muscle is a much more difficult question, and one which is of special significance in view of Hunter's hypothesis that the two types receive entirely different innervations and perform entirely different functions. If such a condition as Hunter suggested be present, then it seems to me a matter of great importance to determine whether the two types remain entirely discrete, or whether the two types are the extreme conditions and all or many intermediate forms exist between them. If the former condition holds good then it is easily conceived how such an innervation of one type by somatic fibres and of the other type by sympathetic fibres could exist. But if the latter condition be present then it seems to me extremely difficult to know how such an innervation could be postulated for the intermediate muscle-fibres between the

two extreme conditions. Such a muscle-fibre would have a function intermediate between the functions of the extreme fibres. How such fibres would be innervated it is difficult to imagine, since Hunter denied the possibility of a double innervation of the individual fibre.

Now this second condition does, I think, occur in vertebrate muscle. All stages between the clear sarcoplasm-poor fibre and the dull sarcoplasm-rich fibre are found in those muscles in which any variation exists. Such a condition is found in the panniculus carnosus. Grützner's figures of the guinea-pig muscle also suggest this, and Cilimbaris stated it definitely for the extrinsic muscles of the eye. Even Kulchitsky's figures, on which much of Hunter's hypothesis rests, do not show a clear distinction into two types of muscle-fibre, and it is significant that Kulchitsky himself did not attempt to make this distinction and made no reference to the size or structure of the muscle-fibres on which his type I and type II endings terminated. In the frog muscle, where the differences are easily demonstrated in a fresh preparation examined in saline, it is not possible always to say to which type the largest of the thin fibres and smaller of thick fibres belong. In connection with another investigation I made cross-sections of the sartorius muscle of the frog and measured the cross-sectional area of each individual muscle-fibre under the same magnification. It is interesting that nearly all the thin fibres were found on the outer surface of the muscle and all the broad fibres beneath this outer layer. Over a number of such experiments it is not possible, in a graph of the frequency of fibres in small groups of nearly similar areas, to state definitely that there are two types of fibres. In the frog's sartorius no definite separation of two types can be made by size, as a gradual transition is found from the smallest to the largest fibres.

In view of these histological considerations it seems to me unlikely that the two *distinct* types of fibre do exist in vertebrate muscle, and on this account that the condition of double innervation as regards a whole muscle only, and a single innervation of the individual fibres, is improbable. Some definite evidence of this last statement has been found. My preparations do demonstrate that the fibres showing marked longitudinal striation and more sarcoplasm are innervated by myelinated nerves and contain endings like those of the mass of fibres which do not show this well-marked longitudinal striation. I do not think that in the panniculus carnosus there are any muscle-fibres which do not have a medullated nerve-fibre ending upon them. According to Hunter's theory the thin muscle-fibres of the frog should be supplied only by the

sympathetic fibres, and as this point is easily established in a number of preparations of frog muscles by the gold chloride method, I have made observations on it. They show conclusively that, neglecting for the moment the sympathetic endings, the thin muscle-fibres do have medullated nerve-fibres ending upon them in small typical end-bushes of Kühne. If a double innervation of frog's muscle exists it must be a double innervation of each individual fibre and not only of the muscle as a whole.

From the functional point of view it is extremely difficult to maintain Hunter's theory as applied to frog's muscle. The two types of frog muscle-fibre have long been known to show two different types of contraction, the large clear fibres giving a quick response and the thin dull fibres a slow sustained response. Hunter maintained, however, that the thin fibres were concerned with plastic tonus, and were innervated solely by sympathetic fibres. Now, since stimulation of the sympathetic, excluding the work of Orbeli to be described later, has always given negative results, and since the two types of contraction have been obtained by stimulation of motor-nerves, it may, I think, be presumed that these two types of contraction have been due to stimulation of somatic fibres. The fact that these two types of contraction have been obtained seems to me to furnish further evidence that the thin fibres have been activated by stimulation of the somatic fibres, and must therefore be innervated by the medullated fibres, whether they have an additional nerve supply through the sympathetic or not. From experiments which are now being conducted I think it may be said definitely that evidence of the two types of muscular action in a frog's gastrocnemius may be seen after removal of the sympathetic chain on one side and stimulation of the ninth and tenth spinal roots above the junction of their respective rami communicantes, thus excluding any possibility of one type of muscle-fibre being innervated solely by the sympathetic.

The work of Kulchitsky is certainly in favour of one set of muscle-fibres being innervated by the sympathetic only. It must, however, be remembered that Kulchitsky's work was done on snake-muscle, which may differ from mammalian muscle. No degeneration experiments have yet been undertaken on snake-muscle to prove the sympathetic nature of the fibres and endings of his type II.

All the other histological evidence, excluding the unpublished work of Hunter and Latham referred to above, is in favour of the double innervation, somatic and sympathetic, of individual muscle-fibres, and my own work certainly supports this theory.

The work of Kahn on the clasping muscles of the frog adds further evidence in favour of the second muscle-fibre having a double innervation. In the season of increased tone, if this function were performed by one type of fibre one would expect an increase in their number, that is, an increase in the number of thin granular fibres. On the contrary he found that the number of fibres was not increased, but that the sarcoplasm of the broad clear fibres was increased in amount.

The nature of the fine non-myelinated fibres, which I have called accessory fibres, must now be considered. It is interesting to recall the six points made by Boeke [9], in which he compared his accessory fibres stained by silver methods with the fine fibres described by Perroncito and Gemelli. This is necessary to see if the term "accessory" may be fitly applied to the non-myelinated fibres I have described in my gold chloride preparations.

(1) The fibres described here are like Boeke's in that they are often single when accompanying a medullated fibre. Fig. 15 is the only noteworthy exception to this, and it shows a single fibre breaking up into a number of branches while accompanying a medullated fibre to a spindle muscle-fibre.

(2) The fibres are shown to be definitely outside the sheath of Henle at certain points, and resemble Boeke's in this respect.

(3) Very small end-plates at a distance from the motor end-plates are formed from the fibres, as Boeke showed.

(4) The great uniformity of Boeke's accessory end-loops cannot be borne out by my preparations,

(5) The granular sole-plates of the accessory end-plates of these fibres have been described, like those of Boeke.

(6) No degeneration experiments have been made.

I think it may be concluded, in spite of (4), that these fibres are identical with those of Boeke, and I have used the term "accessory" with this meaning.

The accessory fibres which pass into the same granular sole-plate as does the medullated fibre cannot be traced out completely after they enter the plate, and so further comparison with the fibres described by Perroncito and Gemelli is not possible.

Boeke, on the basis mainly of his degeneration experiments where the accessory fibres were found intact after the section and degeneration of all the somatic fibres, concluded that the accessory fibres were of sympathetic origin and maintained that the individual muscle-fibre received normally a somatic and sympathetic innervation.

I have made no such degeneration experiments, but I think that some conclusions as to the nature of these fibres may be drawn from my preparations. That they are not branches of the medullated fibres, at least in the muscle, is I think certain, since I found in the intramuscular nerve-bundles and nerves about to enter the muscle a large number of accessory fibres. I hold that they continue down with the medullated fibres and are the same fibres which are seen in the teased specimens of the muscle. The finding of these fine non-myelinated fibres in the muscular nerve is in harmony with the results of Sherrington and Ranson, but not with those of Langley. My only criticism of Langley's work, as I have suggested already, is that I am not convinced that the osmic acid method would show in cross-section or in teased preparations such fine fibres as it is possible to demonstrate with the gold chloride method, especially if these fine fibres are distributed throughout the whole nerve and not confined to one part where they could be seen *en masse*.

The plexus formation of the accessory fibres is of importance in attempting to come to conclusions as to their nature. This plexus formation is totally unlike the somatic fibres and is characteristic of a nervous system of a lower type, the vegetative or sympathetic nervous system as it is seen in vertebrates.

The different terminations of branches of this accessory nerve plexus also throw light on the nature of the fibres forming it. I have been unable to find any difference between the accessory fibres which pass to the capillary wall and those which end on the striated muscle-fibre, and am of opinion that the two types of fibre have exactly the same origin. This seems to me to be demonstrated by such a fortunate specimen as fig. 9, where one branch of the same fibre supplies a capillary wall and the other a muscle-fibre. I have also been unable to find any difference between the accessory fibres and those definitely sympathetic non-myelinated fibres which pass down to the capillaries from the arterioles.

For these reasons, then, I believe that the accessory fibres which I have demonstrated and described belong to the sympathetic nervous system.

Before considering what function these sympathetic fibres may perform, two points are of interest in consideration of their extensive connections with the capillary wall. Besides the usual route of nerve supply to the capillary wall, that is simply an extension of the plexus of pale nerve-fibres found round the arteriole, I have described in muscles a second route, where the non-medullated fibres pass direct

to the capillary wall from the medullated nerve-bundles near the Rouget plate-endings.

Whether these two routes are of physiological significance or not it is difficult to say, but it is not improbable that they may represent the different routes of supply of the two sets of vasomotor nerves, the vaso-constrictors and vaso-dilator fibres. If such be the case it seems more likely that those fibres which pass directly from the medullated fibre bundles are of vaso-dilator function, and come into action with the accompanying spinal motor nerve-fibres. While these suggestions are interesting, they are entirely unsupported by any evidence at the moment.

The other point of interest in relation to the extensive connections of the accessory system with the capillaries, is that whatever function it may have in the striated muscle-fibre, this function must be intimately associated with the vasomotor mechanism. It seems to be difficult to believe that those fibres which pass to the striated muscle could be set in action without the fibres to the capillaries being involved at the same time, and therefore variations in the action of the fibres to the striated muscle will be accompanied by changes in the vasomotor mechanism.

Two possible functions have been suggested for the sympathetic innervation of striated muscle; it may fulfil either a trophic or a tonic function. In 1920, Adrian [1] in a short review of this subject stated: "At present we have only one reason for supposing they have any function at all, and that is the fact that they exist." This followed upon a review of the very contradictory and inconclusive experimental results which had been recorded by a number of workers.

It is worth while to note here that we are dealing with a nerve net, and that we cannot expect to get such a clear picture from our experimental work as we have grown to expect in relation to our work on the synaptic system. In experiments in which the sympathetic rami have been cut or the ganglia removed it is very difficult to know just how much degeneration will take place in a nerve-net of this kind. It seems certain that the degeneration will occur very much more slowly than in the synaptic system if, indeed, much degeneration does occur. It is probable that the nerve-net may be kept intact at least in part by connections which pass to it by way of the blood-vessels. This may account for a number of the failures to get variations in the tone of the muscle after these operations if, indeed, the sympathetic innervation has a tonic function.

Orbeli (1923) [42] alone, on the basis of some work by Ginezinsky, has recently put forward evidence that stimulation of the sympathetic has any effect on striated muscle. In the frog he found that sympathetic stimulation had no added effect during stimulation of the somatic roots to the gastrocnemius while the muscle was responding well, but that after the muscle began to show signs of fatigue sympathetic stimulation gave a definite increase in the response obtained on stimulation of these somatic roots. After a considerable latency the muscle showed increased force, amplitude and rapidity of development of contraction, and the after-effect was prolonged. He therefore thought the action of the sympathetic on skeletal muscle was analogous to the action of the sympathetic on cardiac muscle. As all the vital activities of skeletal muscle are stimulated by the sympathetic, he said the influence of the sympathetic corresponded to that of Pavlov's trophic nerves.

In the experiments of Bottazzi [15], already described, this idea of a trophic function of these sympathetic fibres was not borne out, as after removal of the somatic influence to the diaphragm the muscle degenerated. It is difficult to judge the value of experiments of this or similar nature, for while the sympathetic may have a trophic function, it does not seem to me reasonable to suppose that it will be of such strength as to keep a completely inactive muscle in normal condition.

Sherrington's (1894) [55] observation of muscular nerves in an amyelous fœtus is interesting from this point of view, and also appears to have some relation to a point to be considered later, the persistence of the normal appearance in the spindle muscle-fibres after complete denervation. In this fœtus he found that all the muscular nerves were present, although there was not a single motor spinal nerve-root in any segment of the cord. All the somatic fibres present in the so-called motor-nerves to muscle were sensory. It is of great interest that the striated muscles were normally developed. The trophic influence of the anterior horns must therefore, Sherrington concluded, be in abeyance during fœtal life. He also suggested that the muscular degeneration associated in later life with the section of muscular nerves was due less to a lack of normal trophic influence than to the enforced inactivity of muscles which are accustomed to be active. It is also worthy of note that the sympathetic system was found fully developed and normal.

It may, I think, therefore be considered quite unlikely that, if the sympathetic has a trophic influence on striated muscle, it will be able to exert this influence if the muscle is completely inactive. From the physiology of the peripheral nerve-nets in lower animals (Parker, 1920)

[44] it seems clear that the stimulus to which a nerve-net is most adapted is a mechanical stimulus. It is therefore most probable that whatever the function of the sympathetic in striated muscle, trophic or tonic, it will be influenced mainly by the mechanical stimulus of the movements of the muscle-fibres brought about by the somatic nerve-fibres. It is for this reason, I think, that stimulation of the sympathetic alone has so consistently given negative results.

Whether the sympathetic subserves a trophic function in the striated muscle or not must in view of these considerations be left an open question at present.

The question of the tonic function of the sympathetic in striated muscle is also extremely difficult. It is necessary to consider some of the work that has been put forward to explain its exact mode of action.

Bottazzi (1897) [14] put forward a theory the simplicity of which is attractive. He held that the sarcoplasm of the fibre was responsible for tone, while the striped apparatus or sarcostyles were responsible for rapid movements. This theory was based on observations of the rhythmic changes of tone in the heart of the tortoise, where a very large amount of sarcoplasm was found in one layer of the cardiac muscle cells, and on the supposition that the more specialized movement would be performed by the specialized apparatus—the sarcostyles—and the primitive type of slow movement or tonic contraction would be performed by the unspecialized more primitive sarcoplasm.

This theory is supported by the two different forms of contraction seen in the different types of frog muscle, the fibre showing more sarcoplasm having a longer period of contraction. But the difficulty in this case is that there seems to be some confusion between the normal tone or tonus of the muscle and a prolonged contraction of these thin fibres, what is sometimes described as a "tonic" contraction. It must be proved that the two mechanisms are identical before this piece of evidence really supports Bottazzi's theory.

Kahn's work, already referred to, seems good evidence in favour of Bottazzi's theory. He used a natural seasonal increase in tone and found an anatomical difference in the broad fibres, which showed a marked increase of their sarcoplasm. He did not state that the increased amount of this substance was directly responsible for the increase in tone, but that it was definitely associated with it was clear.

Bayliss (1924) [5] stated "whether the one function is performed by the sarcoplasm, as held by Bottazzi, and the other by the fibrils remains undecided. It is not easy to understand how two fibres of

different function could coalesce with retention by the combined cell of both kinds of innervation, although the case of the salivary glands suggests the possibility." It appears to me that there has been no coalescence of the two fibres of different function, as both types of fibre show both sarcoplasm and sarcostyles, though in different degrees, and it is rather a case of the sarcostyles developing to different degrees from the more primitive sarcoplasm of the individual fibre.

Mosso (1904) [41] stated that he was unable to accept Bottazzi's theory because he did not find that the oscillations of tone were most marked in those fibres which showed a large amount of sarcoplasm, nor were they least marked where the sarcoplasm was only present in a very small degree. He therefore proposed a new theory, based on Perroncito's work, that the tone of the muscle was related to the double innervation of the single muscle-fibre by somatic and sympathetic fibres. He concluded this paper thus: "There is probably in the structure of the muscle one contractile substance which reacts to two excitations, of which the one comes from the myelinated fibres and the other from the fibres of the sympathetic."

On the firmer histological basis of Boeke's work, De Boer (1915) [13] put forward the view that the sarcoplasm innervated by the sympathetic fibres had a tonic function, while the sarcostyles innervated by the somatic fibres were responsible for the rapid movements. It is of interest here that on both the somatic and sympathetic nerve-endings Boeke described his periterminal network, which he thought was connected to the anisotropous substance of the sarcostyles. He does not state definitely whether the periterminal network of the accessory fibre was also connected with the sarcostyles; if it, like the medullated fibre's network, is connected with the sarcostyles, then De Boer's theory cannot be accepted.

Langelaan (1915) [38] and (1922) [39] carried De Boer's theory further. He distinguished two different components of muscle tone, the plastic and the contractile factors. The plasticity of the muscle he described as that property by which any change in the length of the muscle caused by external forces was rendered permanent to some degree. The greater the degree of plasticity, the greater is the permanent deformation. It is evident that such a permanent deformation will not be accompanied by a continued expenditure of energy nor by electrical phenomena, or at least the expenditure of energy will be extremely small. This plasticity he thought was intimately associated with the trophic state of the muscle, and the degree of plasticity may

prove to be a measure of the trophic state. Plastic tonus is a reflex tonus which shows itself after movements and not during them. It is concerned with attitude and posture. Contractile tonus, on the other hand, is the slight degree of contraction in the muscle, and is, he maintained, the component which Brondgeest in his classical experiment demonstrated. This, unlike the plastic tonus, is not a state of equilibrium and is accompanied by an expenditure of free energy and by rhythmic electrical phenomena. It is associated with the production of heat in muscle.

From Boeke's demonstration of the sympathetic fibres in muscle, Langelaan put forward the theory that the plastic component of muscle-tonus is the property of the sarcoplasm and is under the control of the sympathetic system, and the contractile component of muscle-tonus is the property of the striped apparatus of the fibre and is under the control of the cerebrospinal system.

This hypothesis of Langelaan includes and extends the theories of both Bottazzi and De Boer, and in many ways clears up the conflicting results of other workers. Mosso's criticism of Bottazzi is now of little value, as he was evidently referring to contractile tonus and not to plastic tonus. That the sympathetic alone is concerned with muscle tone, as De Boer held, may be abandoned in view of much of the experimental work and of Langelaan's more complete exposition. The negative results of many of the workers, after extirpation of the sympathetic or section of the rami communicantes, is explained by the fact that they were attempting to get changes in the contractile component and not in the plastic compound of the muscle-tonus. It also fits in with the view that the nerve-net is more adapted to a mechanical stimulus. While there are points in this hypothesis which are not yet clear, it appears to me to fit the known facts best. Langelaan's hypothesis is also correlated to Orbeli's work, in that Langelaan suggested that the degree of plasticity may be an index of the trophic state of the muscle.

Hunter (1925) [33] is in agreement with Langelaan in the distinction of the two components of muscle-tonus, but differs in this that he, on the basis of the idea of Grützner (1887) [30] of the " inner support " of the red fibres in a mixed muscle, attributed the two components to different muscle-fibres. The reasons for not accepting this hypothesis have already been given, the unproved existence of the two distinct types of muscle-fibre in all vertebrate striped muscle, and the certain innervation of the sarcoplasm-rich fibres in some muscles by medullated

fibres. Hunter and Royle, however, did clearly demonstrate the loss of plasticity in the muscle after removal of the sympathetic influence. They found that the longer the period after sympathetic ramisectomy the clearer was this demonstration, which may have some relation to the length of time required to get marked degeneration in the nerve-net of the non-myelinated fibres in the muscle.

The action of adrenalin has as yet given little aid in the solution of this problem. It cannot be expected, in view of Langelaan's hypothesis, that it should show any direct action on muscle. All that might be expected is that it would increase the plasticity of the muscle after stimulation. There is some slight evidence in favour of this.

The reflex origin of muscle-tonus is undoubted, and it must, I think, be in some way related to the neuro-muscular spindles. The exact function of these structures has not yet been ascertained; it has been suggested that they are related to proprioceptive sensation. I think it may be taken that they are supplied with three types of nerve-fibre: the main sensory fibres, the motor-fibres and the accessory fibres, and any attempt to interpret their function must take cognizance of these three sets of fibres. My results do not confirm Kulchitsky's observations in the snake muscle, where he found the end-plate of the spindle muscle-fibres to be formed from sympathetic fibres. In the hedgehog and in man I have found the end-plates formed from medullated fibres. Sherrington [55] revealed the fact that complete denervation does not cause degeneration of the spindle muscle-fibres. In view of his suggestion, following his description of the amyelous fœtus, that it was only after the muscle had been active, that is after birth, that section of the muscular nerve caused degeneration, and that this was probably due to inactivity, it seems possible that the spindle muscle-fibres have never been accustomed to movements like those of the ordinary muscle-fibres, and so they do not degenerate upon section of the nerve. Sherrington [55] was of opinion that these muscle-fibres responded to a mechanical stimulus only, as he maintained they had no motor nerve-fibres. This mechanical stimulus was the movement of the mass of fibres surrounding them. I do, however, believe that they have motor-fibres and that they respond to nervous and not mechanical stimuli, which may be of reflex origin. In those muscles which do not show any marked variation on their ordinary muscle-fibres, the spindle muscle-fibres are certainly as a rule clearly distinct from the ordinary muscle-fibres, being thinner and richer in sarcoplasm. These, I think, represent the thin fibres of the frog muscles, where the thin spindle muscle-fibre lies free in the mass of the muscle and has little or no capsule.

Sherrington [55] described an interesting experiment which he thought threw some light on the action of these spindle muscle-fibres. Forty-two days after section of the ventral roots the muscles retained some degree of response to faradic stimulation. Fairly strong stimulations applied to the nerve of such a muscle caused no muscular response, but very strong stimulation resulted in a peculiar slow, feeble, steady contraction lasting for five seconds after stimulation ceased. Crushing of the nerve peripheral to the point of stimulation stopped the phenomenon, and it was not obtained after excising the spinal ganglion. It had nothing to do with regeneration of the nerve-fibres. He added, "It is tempting to relate it to the intrafusal muscle-fibres." These muscle-fibres would certainly have normal appearances, and it may be that this contraction was a reflex through the spinal ganglion and passing out by the sympathetic fibres. It is difficult to see how this contraction, if it is due to the contraction of the spindle muscle-fibres, could be set up by a mechanical stimulus, as the ordinary muscle-fibres would be degenerated and could not react sufficiently to give a mechanical stimulus to the spindle.

The annulo-spiral ending of the spindle seems specially adapted to receive impressions of varying cross-sectional area of these spindle muscle-fibres, such as would result from a wave of contraction in these fibres. The afferent impulses set up in this way may be either of proprioceptive nature, or be the afferent impulses of a tonic reflex arc. The thick capsule round the region of the annulo-spiral endings and the periaxial lymph space seem to be special adaptations to ensure that the sensory fibres will only be acted upon by the action of the spindle muscle-fibres, and not by the pressure of the contraction of the ordinary muscle-fibres.

I wish to acknowledge my indebtedness to Professor Camillo Golgi, in whose laboratory I learned the method used in this research, and who by his kind and helpful attention made it possible for me to attempt this work. I have also to thank Professor D. Noël Paton and the Staff of the Institute of Physiology for their unceasing interest, which has been an inspiration to me through the whole period of my work.

V.—Conclusions.

(1) The muscle-fibres of the panniculus carnosus of the hedgehog show varying degrees of longitudinal striation and varying contents of sarcoplasm, but cannot be divided into two definite classes.

(2) The nerves entering the muscle contain a large number of very fine non-myelinated nerve-fibres.

(3) The motor end-plates show great variations in size, form and shape, but cannot be classed into two definite types.

(4) The individual muscle-fibres are plurisegmentally innervated, in a slightly different manner from that which Agduhr demonstrated in limb muscles.

(5) All the muscle-fibres, whether rich or poor in sarcoplasm, appear to be innervated in exactly the same way. It is certain that the sarcoplasm-rich fibres are innervated by medullated nerves.

(6) The presence of Boeke's accessory fibres and endings can be confirmed. They appear to be a system of fibres completely separate from the somatic fibres and are apparently of sympathetic origin.

(7) The accessory fibres have been seen to end in some cases on a muscle-fibre which is also supplied by a medullated fibre.

(8) The accessory fibres show connections with the capillary wall, and two different routes of nerve supply to the capillaries are demonstrated, one by extension from the arteriole and the other direct by way of the motor nerve-fibres.

(9) The plate-endings on the spindle muscle-fibres are formed from definitely medullated nerve-fibres.

(10) In frog muscle the thin and thick muscle-fibres are both supplied by medullated motor nerve-fibres; in many cases one medullated fibre supplies both types of muscle-fibre.

(11) Extremely little variation exists in the size and structure of the muscle-fibres of human pectoral muscles.

(12) Accessory fibres are present in the frog, lizard, and human muscle.

(13) The plate-like endings on the human muscle-spindles are formed from medullated fibres.

VI.—Description of Figures.

The drawings have been made with a camera lucida, as photographs are of very little value on account of the varying levels of the structures in teased preparations. The figures in the drawings refer only to the number of the slide.

Figs. 1 to 16 are from the panniculus carnosus of hedgehog.

Fig. 1.—A dissociated muscle-fibre of the panniculus carnosus, showing two motor end-plates on the same muscle-fibre a long distance apart. An example of the plurisegmental innervation of an individual fibre.

FIG. 2.—A small intramuscular nerve-bundle showing the presence of accessory fibres at some distance from the terminations of the medullated fibres of this bundle.

FIG. 3.—Three motor end-plates of different sizes. The two small plates shown in profile receive fibres which are non-medullated near the plates, but are medullated further up the small nerve-bundle.

FIG. 4.—Two motor end-plates of different size formed from branches of the same medullated fibre. Small plate in profile.

FIG. 5.—Three motor end-plates, the lowest of which shows a fine non-myelinated fibre arising just proximal to the entrance of its nerve-fibre into the muscle. The nature of this fibre is difficult to determine; its accessory nature may be hidden, or it may be simply a collateral.

FIG. 6.—A motor end-plate, showing an ultra-terminal fibre which passes out from the terminal ramifications to the right, runs downwards and rises to reach a different level and then passes to the left. It forms a small end-arborization which lies either on the opposite side of the small muscle-fibre or on another fibre.

FIG. 7.—A very fine non-myelinated fibre whose nature is not definitely seen. The ending probably lies between the muscle-fibres. The medullated fibre passes upwards to form a motor-plate which is obscured by very deep staining.

FIG. 8.—Two medullated fibres passing upwards to form motor end-plates. Between them and lying outside the sheath of Henle, which is shaded lies an accessory fibre, which ends by passing to the motor-plate on the right. (Accessory fibre of first type.) Capillaries—stippled.

FIG. 9.—An accessory fibre of the second type which passes across from the nerve-bundle on the right to form an accessory plate, seen in profile on a large muscle-fibre. The thickening just as it leaves the nerve-bundle is a deeply-stained nucleus. The accessory fibre divides into very fine branches which form the ending. One of the fine branches passes downwards to become intimately connected with the wall of a capillary. Capillaries—stippled. (The horizontal capillary passes over the end-plate and is not drawn in full to give a clearer picture.)

FIG. 10.—Plexus of accessory fibres. One of these ends in a small plate at the foot of the drawing. This fibre lies at a different level from the one which it crosses over.

FIG. 11.—Plexus of accessory fibres. The exact termination of many of the plexus branches is not clear, but one can be seen forming an end-plate on a narrow muscle-fibre, which on being traced out is found to be the tapering end of a large fibre. Another branch may be seen passing to a capillary. Capillaries—stippled.

FIG. 12.—Plexus of accessory fibres.

FIG. 13.—An accessory fibre passes down with a thick medullated fibre. It appears to branch and some of the branches appear to end round or in the motor-plates, while others pass definitely to capillary walls. Capillaries—half tone.

FIG. 14.—An accessory fibre of the third type which passes to a capillary wall. The course of the accessory fibre over the plate is obscured. It runs close to but does not, I think, supply the capillary on the left, but it certainly supplies the capillary on the right. Capillaries—stippled.

FIG. 15.—A thick medullated fibre from a motor nerve branch, which passes to form a plate on a spindle muscle-fibre. It is accompanied by an accessory fibre which divides up into a large number of fibres which branch and reunite among themselves. These accessory fibres cannot, unfortunately, be followed in this preparation; some of them are torn. Motor end-plates below faintly shaded.

FIG. 16.—One end of a spindle muscle-fibre. The cross-striping is diagrammatic. A medullated fibre is seen to end in three plates on the muscle-fibre. Accompanying it is an accessory fibre of the third type passing to end in relation with capillaries. Capillaries—stippled.

FIG. 17.—Frog muscle. One thick muscle-fibre and two very thin muscle-fibres supplied by one medullated nerve-fibre. All three endings are typical Kühne endings, those of the smaller muscle-fibres being in no way different, except that they are smaller.

REFERENCES.

[1] ADRIAN. *Med. Science*, 1920, **2**, 454.
[2] AGDUHR. *Anat. Anz.*, 1916, **49**, 1.
[3] *Idem. Ibid.*, 1919, **52**, 273.
[4] *Idem. Proc. Kon. Akad. v. Wet. t. Amsterdam*, 1918, **21**, 1231.
[5] BAYLISS. "Principles of General Physiology," 4th edition, 1924, p. 546.
[6] BOEKE. *Verslag. Kon. Akad. v. Wet. t. Amsterdam*, April, 1909.
[7] *Idem. Anat. Anz.*, 1909, **35**, 193.
[8] *Idem. Ibid.*, 1910, **35**, 481.
[9] *Idem. Ibid.*, 1913, **44**, 343.
[10] *Idem. Verh. d. Kon. Akad. v. Wet. t. Amsterdam*, 1916-17, **18**, 91, and **19**, 1.
[11] *Idem. Brain*, 1921, **44**, 1.
[12] BOEKE and DE BARENNE. *Proc. Kon. Akad. v. Wet. t. Amsterdam*, 1919, **21**, 1227.
[13] DE BOER. *Zeitschr. f. Biol.*, 1915, **65**, 239.
[14] BOTTAZZI. *Journ. Physiol.*, 1897, **21**, 1.
[15] *Idem. Quart. Journ. Exper. Phys.*, supplementary vol. 1923, **66**.
[16] BOTEZAT. *Zeitschr. f. Wiss. Zool.*, 1906, **84**, 228.
[17] *Idem. Anat. Anz.*, 1910, **35**, 396.
[18] BREMER. *Arch. f. Mikr. Anat.*, 1882, **21**, 169.
[19] CECCHERELLI. *Monitore Zool. Ital.*, 1902, **13**, 9.
[20] CILIMBARIS. *Arch. f. Mikr. Anat.*, 1910, **75**, 692.
[21] DART. *Journ. Comp. Neur.*, 1924, **36**, 441.
[22] DOGIEL. *Arch. f. Mikr. Anat.*, 1902, **59**, 1.
[23] FUSARI. *Arch. Ital. de Biol.*, 1903, **39**, 473.
[24] *Idem. Ibid.*, 1907, **48**, 472.
[25] GEMELLI. *Monitore Zool. Ital.*, 1906, **17**.
[26] GOLGI. "Opera Omnia," 1903, **1**, 211.
[27] *Idem.* "Dispense di Istologia," Parte Generale, anno 1919-20, 188.
[28] GRABOWER. *Arch. f. Mikr. Anat.*, 1902, **60**, 1.
[29] GRÜTZNER. *Rec. Zool. Suisse*, 1884, **1**, 665.
[30] *Idem. Arch. f. d. g. Physiol.*, 1887, **41**, 280.
[31] HUBER. *Anat. Anz.*, 1899, **15**, 335.
[32] HUBER and DE WITT. *Journ. Comp. Neur.*, 1897, **7**, 4.
*[33] HUNTER. *Brit. Med. Journ.*, 1925, **1**, 197.
[34] KAHN. *Arch. f. d. g. Physiol.*, 1924, **205**, 381.
[35] KULCHITSKY. *Journ. Anat.*, 1924, **58**, 152.
[36] *Idem. Ibid.*, 1924, **59**, 1.
[37] KUNTZ and KORPER. *Proc. Exper. Biol. and Med.*, 1924, **22**, 23.
[38] LANGELAAN. *Brain*, 1915, **38**, 235.
[39] *Idem. Ibid.*, 1922, **45**, 434.
[40] LANGLEY. *Journ. Phys.*, 1922, **56**, 382.

* This reference to the lectures which Hunter had prepared but unfortunately did not deliver, is given in preference to the published original papers, as more details are given of the histological basis of his work.

[41] Mosso. *Arch. Ital. de Biol.*, 1904, **41**, 183.
[42] Orbeli. *Journ. Petrograd Med. Inst.*, 1923, **6**, 8.

Reviewed by:—

[43] Walshe. *Med. Science*, 1924, **10**, 486.
[44] Parker. "The Elementary Nervous System," 1920.
[45] Pembrey. *Journ. Phys.*, 1903, **29**, 195.
[46] Perroncito. *Arch. Ital. de Biol.*, 1901, **36**, 245.
[47] *Idem. Ibid.*, 1902, **38**, 393.
[48] Ransom. *Amer. Journ. Anat.*, 1911, **12**, 67.
[49] Ranvier. *Compt. rend.*, 1887, **104**, 79, and 1888, **107**, 971.
[50] Retzius. "Biologische Untersuchungen," Neue Folge, 1892, **3**, 48.
[51] Ffrangcon Roberts. *Brain*, 1916, **39**, 297.
[52] Ruffini. *Journ. Phys.*, 1898-99, **23**, 190.
[53] *Idem. Riv. di patol. nerv. e ment.*, 1900, **5**.
[54] Schäfer. "Quain's Anatomy," 1912, vol. ii, part 1, p. 190.
[55] Sherrington. *Journ. Phys.*, 1894, **17**, 211.
[56] Sutton. *Amer. Journ. Anat.*, 1915, **18**, 117.
[57] Tschiriew. *Arch. de Phys. Nerv. et Path.*, 1879, **6**.
[58] Wilson. *Brain*, 1921, **44**, 237.

Notices of Recent Publications.

Myelogenetisch-anatomische Untersuchungen über den Zentralen Abschnitt der Sehleitung. Von R. A. Pfeifer. Berlin: J. Springer. 1925. Price 18 marks.

Of no other region of the brain perhaps has our knowledge of the anatomy, physiology and functional arrangements increased so much within recent times as of the visual system. Thanks mainly to clinical and pathological investigations we have within the last few years learned accurately the cortical extent of the perceptive visual area, and even the local representation within it to different zones of the retinæ.

The exact anatomy of the optic radiations, that is of the corticopetal visual pathway, has still remained, however, a matter of dispute. It is to this subject that Pfeifer's monograph is devoted. He has relied almost wholly on the myelinization method of Flechsig, arguing that it is in the first place the most natural means of examination, and in the second that as it gives positive rather than negative pictures observations made by it can be more easily and safely interpreted. He has also made use of an ingenious method of constructing models, numerous photographs of which illustrate his book and facilitate the interpretation of his descriptions.

Undoubtedly the most valuable part of his work is the detailed description of the anatomy and relations of the fibres of the radiations. Some of his conclusions may require control, but there can be little doubt that they are on the whole correct. The considerable variations which he has found in their course and arrangement may be important in explaining certain clinical observations. On the other hand his attempt to localize different categories of fibres within the radiations is less convincing; in some instances it is difficult to follow his arguments, and in others his views run counter to available evidence. He describes, for instance, a bundle of macular fibres which leaves the radiations of one side, crosses in the corpus callosum and terminates in the opposite visual area. The work described here is, however, an important contribution to our knowledge and will also serve to stimulate investigations into points which are not yet settled.

Kompendium der Topischen Gehirn-und Rückenmarksdiagnostik. Von Robert Bing. 6te Auflage. S. 242. Berlin and Wien: Urban and Schwarzenberg. 1925. Price 9.90 marks.

The special feature of the sixth edition of Bing's well-known book is the greater wealth of illustrations that it contains; some are wholly new, others are old figures which have been redrawn or modified. The use of colours in

many of the figures makes them more easily intelligible to those not intimately acquainted with the anatomy of the central nervous system.

The value of this book to students of organic neurology is already fully recognized; the improvements which it has undergone in this edition will increase its usefulness.

Sciatica, or Myopathia e Labore of the Posterior Region of the Leg. By JOHANNES HELWEG. Pp. 216. Copenhagen: Arnold Busck. London: Lewis and Co. 1925.

This monograph, which was published in Danish a few years ago, is now translated into English. The author's aim is to prove that the usually accepted view that sciatica is a neuralgia or neuritis of the sciatic nerve is incorrect, and to demonstrate that the symptoms are due to a primary affection of the muscles. His argument is that long continued use of any muscle, or a sudden unwonted strain upon it, leads to pathological fatigue, that is to the accumulation within the muscle of fatigue products to such an extent that they are not removed after a normal period of rest and consequently produce pathological changes in the muscle fibres. It is to this permanent affection of the muscles that the author applies the term *myopathia e labore*. It is true he admits that sciatica is often associated with lesions in the joints, bones or other surrounding tissues, but these are only predisposing factors in so far as they involve extra strain upon the muscles of the buttocks and thighs.

In support of this thesis the author states that areas of increased consistence and tenderness can be always found by proper palpation in the muscles of the limb, and it is to these changes in the muscles that he attributes Valleix's tender points, Lasègue's sign, wasting, absence of ankle-jerk and changes in the electrical reactions, when these are present. Disturbances in sensation may be due to compression of the sensory nerves by the local hardenings of the muscles. The theory is expanded to include all relevant phenomena and to explain many symptoms that it obviously accounts for.

Mind and Medicine. By T. W. SALMON. New York: Columbia University Press. London: H. Milford. 1924. Price 5s.

This short address emphasizes the unsatisfactory attitude of medicine towards the study of the mind and of mental disorders, and the necessity of educating the medical student in modern psychology and psychopathology.

The present neglect of psychological factors in disease is due to an assumed parallelism between mind and body, and the attitude which regards it as unscientific to study psychological phenomena until they can be described in terms of anatomy, physiology, and biochemistry. The author in this interesting and suggestive lecture pleads that the science of medicine should extend to mental abnormalities equally as it does to physical disorders.

The Emotions, Morality and the Brain. By C. von Monakow. English Translation by Barnes and Jelliffe. Nervous and Mental Disease, Monograph Series. No. 39. Washington and New York. 1925. Price 2 dollars.

Many English readers are already acquainted with von Monakow's psychological essays and the general tend of his views which are, as might be expected, determined or at least influenced by his lifelong work on the anatomy, physiology, and pathology of the nervous system. The monograph of which this is the English translation is one of the most important of the psychological articles which he has written; its chief interest, perhaps, is the author's conception of the material components and physical basis of the emotions, and his discussion of their pathology. The chapter on anatomical structure and physiological functions is a striking review by one who has been primarily an anatomist and physiologist of the mode of action of the variously combined elements of the nervous system.

The translators confess that the "tendency of the English language to simplify and almost to emasculate the psychical tension of German thought has been here resisted," and that they have left the matter in its apparently confused form is only too true. Von Monakow's German style is undoubtedly complicated, but this only makes more urgent the duty of expressing his ideas in another language in an easily comprehensible form.

The book consequently requires careful study and the expenditure of considerable time, but it well repays both.

Studies in Psychiatry. Vol. II. By Members of the New York Psychiatrical Society. Pp. 233. Nervous and Mental Disease Publishing Co., Washington and New York. London: H. Milord. 1925.

The New York Psychiatrical Society has previously published another volume of Studies, which is now out of print. This volume contains a selection of papers read at different times, many of which are in themselves valuable contributions to psychiatry, while others will serve mainly to illustrate the lines of development favoured by the authors. A few titles will serve to indicate the contents of the volume, as Macfie Campbell's paper "On the Mechanism of Convulsive Disorders and Allied Symptoms," and "On the Mechanism of Some Cases of Manic-depressive Excitement"; Knapp, "On the Treatment of Mental Disorders"; Adolf Meyer, "On Objective Psychology or Psychobiology"; and Lambert, "On the Clinical and Anatomical Features of Alzheimer's Disease."

The Development of Psycho-analysis. By S. Ferenczi and Otto Rank. English Translation. Pp. 68. New York and Washington Publishing Co. 1925.

Psycho-analysis and the Psychic Disorders of General Paralysis. By S. Hollós and S. Ferenczi. English Translation. Pp. 48. New York and Washington Publishing Co. 1925.

Several of the recent publications, as these two, of the Nervous and Mental Disease Monograph Series, have been translations into English of articles or books which originally appeared in another language.

The first of these monographs, "by Professor Freud's most brilliant and original followers," is of interest as a sketch of the development of the technique of the psycho-analytic cult and an estimate of its future prospects; it will appeal to all interested in the growth and gradual expanse of a theory which cannot be rigidly controlled by facts, and not only to serious students of psycho-analysis as the translator believes.

The second booklet illustrates the progressive tendency of the psycho-analysts and the ease with which a theory can be extended to the explanation of all manner of phenomena. The final paragraph expresses the belief "that psycho-analysis, which hitherto has declared itself competent only for an understanding of the so-called functional psychoses, now deserves consideration also in organic psychiatry."

Zum Gegenwärtige Stand der Lehre von den Reflexen. By M. Minkowski. Neurologische und psychiatrische Abhandlungen aus dem Schweizer Archiv für Neurologie und Psychiatrie. Pp. 61. Zürich: Verlag Orell Füssli. 1925.

The author gives a brief but comprehensive review of our knowledge of reflex action in general and of certain reflex reactions in particular, embodying both experimental and clinical observations in his account. In his opening chapter he discusses the history of the conception of reflex action from the time of Descartes to that of Sherrington and Magnus. A phylogenetic and ontogenetic study of the evolution of reflex reactions then follows, such reactions in primitive animal forms and in the human fœtus and newly-born child illustrating the author's account. From the development of co-ordination by reflex action he passes to the co-ordination of reflex actions themselves, describing briefly examples of these two grades of co-ordination to be found in the work of Sherrington, Magnus and others. A short chapter is devoted to the work of Pawlow on the "conditioned reflex," and another to certain visceral reflexes.

Having traced the evolution of reflex action, the author proceeds to the analysis of reflex reactions as these are revealed to observation in various stages of dissolution of nervous activity, and in doing so he pays tribute to Hughlings Jackson's masterly teachings on this subject. The appearance of various reactions, as "release phenomena," is discussed, and the parts played by diaschisis and by evolution in the modification of reactions thus revealed are considered. Various examples are taken from the experimental and spinal preparations and from clinical neurology to illustrate these points. A final chapter deals with the relationship of instinct with reflex reaction. He believes

this relationship to be of the closest, the difference between the two being one of complexity only. Thus certain instinctive reactions are regarded by biologists as complex chain-reflexes, the simple reflex reaction being essentially a fragmentary component of the more complex reaction. There is an extensive bibliography.

Physiology of the Central Nervous System and Special Senses. By N. J. Vazifdar. Bombay: Govind and Co.

This little book is an outline of the anatomy and physiology of the nervous system, based upon standard textbooks and authorities. The author has succeeded in preparing a concentrated and detailed account of his subject without being exhaustive or obscure. Controversial statements are in the majority of cases wisely omitted. The object of the book is to assist Indian medical students in their examinations and it should amply fulfil this aim. The illustrations, however, are scarcely worthy of the book, being in the most part somewhat crude and badly printed. A brief bibliography at the end of each chapter would add to the value of the work, by indicating to the more inquiring student some of the standard references to the subject in question.

The Inheritance of Mental Diseases. By Abraham Myerson. Pp. 336. Baltimore: Williams and Wilkins. London: Baillière, Tindall and Cox. 1925. Price 25s.

The author recognizes the difficulty in his task of attempting to elucidate the laws and conditions that determine the transmission of phenomena so ill-defined as mental diseases, but he has produced a book which will interest psychiatrists, sociologists and biologists, though certainly many of its statements and conclusions will not receive their approval. One of its most striking features is the individual line taken up by the author, who relies almost entirely on his personal experience, though he cites numerous other writers and provides a very extensive bibliography.

The first hundred pages are devoted to a review of the current theories of heredity and of mental diseases, written in such general terms as to suggest its intention of instructing non-medical readers in the essential rudiments of these subjects. The remaining pages are based mainly on his own observations, though experimental and other work tending to support his conclusions is liberally quoted. The rest of the book treats of the main subject chiefly under the headings of vertical and horizontal (this is through siblings and collaterals) transmission of specific mental diseases. His main conclusion is that mental diseases are not transmitted as hereditary characters but are abnormalities caused by unknown agents, the effects of which may persist over two or more generations and then die out. In fact the hypothesis held by Forel and others that the germinal cells may be injured by poisons, as alcohol, and other external factors, and that the injury to the germ plasm is inheritable, is the hypothesis

which he believes best explains his facts. He therefore lays more weight on exogenous factors, as unfavourable environment, than on true intrinsic defects in the propagation of mental diseases.

Clinical Psychology. By L. E. Bisch. Pp. xiv. + 346. Baltimore: Williams and Wilkins. London: Baillière, Tindall and Cox. 1925. Price 15s.

This book has a misleading title; it is not, in the ordinary sense of the term, a textbook of clinical psychology, but an outline of psychopathology as applied to abnormal children. It has apparently grown from a series of lectures delivered by the author to students at a teachers' college, and its primary aim is to give the school teacher a working basis by means of which he may be able to recognize and deal with atypical children in the class-room.

It can scarcely be claimed that even with this as its scope the book is a success; much of it is too complicated and too heavily laden with medical terms to be easily intelligible to the ordinary lay teacher, and on the other hand it has little new to offer to medical men, even to those not intimately acquainted with the subjects with which it deals. Several plates are included to illustrate types of defective children and some of the commoner psychoses, but even these are not very satisfactory.

Manual of Psychiatry. By P. E. Bowers. Pp. 364. Philadelphia and London: Saunders and Co. 1925. Price 18s.

This textbook has been written for the student and general practitioner rather than for those with some knowledge of, or engaged in, the study of mental disorders. It is fairly comprehensive for a book of its size, and is so systematic and concise that a surprising bulk of information is contained in its pages. The chapters on the toxic psychoses and on the symptoms of mental disorders are among the most satisfactory, but those devoted to dementia præcox and the paranoid states are not worthy of the importance of those subjects.

The description of the methods of examination and the discussion on the relationship of insanity to crime will be particularly helpful to the general practitioner for whom the book is primarily intended.

Collected Papers. By S. Freud. English Translation. Vol. III.—Case Histories. Pp. 607. London: Hogarth Press. 1925. Price 30s.

This, the third volume of Professor Freud's collected works, which is now translated into English and published by the Institute of Psycho-analysis, contains only five long case records and comments on the facts brought out by analysis.

The translators have done their work excellently and produced a book in very readable English.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I to XXIII inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.